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Prevalence, clinical correlates and prognostic significance of heart failure with preserved ejection fraction in systemic sclerosis.

Ana Leonor Rei Escaleira

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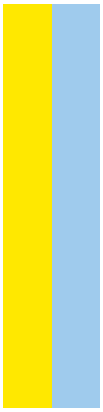

Prevalence, clinical correlates and prognostic significance of heart failure with preserved ejection fraction in systemic sclerosis.

Dissertação de candidatura ao grau de Mestre em Medicina submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

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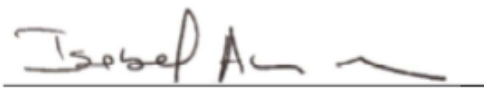

(Professora Doutora Isabel Maria Pereira Alves de Almeida)

Porto, junho de 2020

Dedication

À Família, por me continuar a ensinar “o amor pelas coisas belas”.
Aos Avós, o melhor do mundo e permanente fonte de inspiração.
Aos meus Amigos, que transformaram o ICBAS na minha nova casa e me fizeram viajar tantas vezes, sem sair do bairro.
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Por fim, mas não menos importante, um especial agradecimento à Doutora Marta Fontes Oliveira, cuja disponibilidade, dedicação e empenho permitiram continuar a enriquecer este projeto.

RESUMO

Introdução: O envolvimento cardíaco primário nos doentes com Esclerose Sistémica (SSc) tem vindo a ser progressivamente reconhecido como uma complicação clínica relevante. O presente estudo propôs-se determinar a prevalência, correlações clínicas e o significado prognóstico da Insuficiência Cardíaca com Fração de Ejeção Preservada (HFpEF) numa população de doentes com Esclerose Sistémica.

Métodos: Estudo retrospetivo observacional. Todos os dados foram obtidos através da revisão dos processos clínicos eletrónicos dos doentes com os diagnósticos de Esclerose Sistémica e Esclerose Sistémica Muito Precoce que realizaram Ecocardiograma. Definiu-se HFpEF como a presença de dispneia de esforço e de alterações cardíacas estruturais anormais (hipertrofia ventricular esquerda ou alargamento da aurícula esquerda), com preservação da função de ejeção do ventrículo esquerdo. O modelo de riscos proporcionais de Cox foi utilizado para analisar a associação entre HFpEF e todas as causas de mortalidade.

Resultados: Dos 180 doentes com diagnóstico de Esclerose Sistémica incluídos no estudo (idade média 54±15 anos; 92% sexo feminino), a maioria apresentava subtipo cutâneo limitado (70%) com uma duração média de evolução da doença de 11 anos. A prevalência global de HFpEF foi de 26%. Estes doentes eram mais velhos, tinham maior probabilidade de apresentar Doença Intersticial Pulmonar (ILD), maior prevalência de Hipertensão Arterial e de Fibrilhação Auricular e níveis aumentados de NT-proBNP. Ao longo de um período de seguimento médio de 10 anos [5.9-13.5 anos], 12 (7%) doentes morreram. Os doentes com Esclerose Sistémica que apresentavam HFpEF tinham um aumento do risco de mortalidade de 2.5 vezes (HR 4.26, 95% CI 1.34 – 13.48, p=0.01). Após ajustarmos para a idade, a estimativa de associação continuava a assinalar um risco aumentado, mas não se revelou estatisticamente significativa (HR 3.13, 95% CI: 0.98-9.95 p=0.05).

Conclusão: Numa grande coorte de doentes com Esclerose Sistémica, verificamos uma prevalência significativa de HFpEF, que se associava a factores de risco cardiovasculares e fibrilhação auricular, bem como à presença de envolvimento pulmonar (ILD). Mais importante, o diagnóstico de HFpEF nestes doentes sinalizava uma tendência de aumento do risco de morte. Estes resultados reforçam a importância do reconhecimento da HFpEF como um marcador de mau prognóstico nesta população.

Palavras-Chave: Insuficiência Cardíaca com fração de ejeção preservada, Esclerose Sistémica.

ABSTRACT

Introduction: Primary cardiomyopathy is progressively being recognised as a clinically relevant complication of systemic sclerosis (SSc). We aimed to examine the prevalence, clinical correlates and prognostic significance of heart failure with preserved ejection fraction (HFpEF) in an SSc population.

Methods: We retrospectively collected data from SSc and VEDOSS patients who had undergone echocardiography. HFpEF was defined by the presence of exertional dyspnea and abnormal cardiac structure (left ventricular hypertrophy or left atrium enlargement) with preserved left ventricular ejection fraction. Cox proportional hazards regression model was used to analyse the association between HFpEF and all-cause mortality.

Results: Of the 180 SSc patients included (mean age 54±15 years; 92% female), most had a limited SSc subtype (70%) with a mean disease duration of 11 years. The global prevalence of HFpEF was 26%. These patients were older, more likely to have interstitial lung disease (ILD), had a higher prevalence of hypertension and atrial fibrillation and had increased NT-proBNP levels. Over a median follow-up of 10 years [5.9-13.5 years], 12 (7%) of the patients died. SSc patients with HFpEF had a 2.5-fold increased risk of dying (HR 4.26, 95% CI 1.34 – 13.48, p=0.01). After adjusting for age, the association estimate still signaled an increased risk but it was not statistically significant (HR 3.13, 95% CI: 0.98-9.95 p=0.05).

Conclusion: In a large SSc cohort, the prevalence of HFpEF was significant; it was associated with cardiovascular risk factors and atrial fibrillation, as well as with SSc-related lung involvement. Importantly, HFpEF signalled an increased risk of dying. This highlights the importance of recognising HFpEF as a marker of poor prognosis in this population.

Keywords: Heart Failure with Preserved Ejection Fraction, Systemic Sclerosis.

List of Abbreviations

AAS: Acetylsalicylic acid (aspirin)
ACA: Anti-centrome antibodies
ACEI/ARB: Angiotensin-converting-enzyme inhibitor/Angiotensin II receptor blocker
ACR-EULAR: American College of Rheumatology - European League Against Rheumatism
BMI: Body mass index
dcSSc: Diffuse cutaneous systemic sclerosis
DLCO/SB: Diffusing capacity of the lung for carbon monoxide/Single breath
DLCO/VA: Diffusing capacity of the lung for carbon monoxide/Total alveolar volume
DLCO: Diffusing capacity of the lung for carbon monoxide
FEV1: Volume of air forcibly expired in the first second
FVC: Forced vital capacity
HF: Heart failure
HFpEF: Heart failure with preserved ejection fraction
Hg: Hemoglobin
ILD: Interstitial Lung Disease
LAE: Left atrial enlargement
lcSSc: Limited cutaneous systemic sclerosis
LVEF: Left ventricle ejection fraction
LVH: Left ventricle hypertrophy
NT-proBNP: N-terminal pro-B-type natriuretic peptide
PAH: Pulmonary Arterial Hypertension
SD: Standard deviation
SSc: Systemic Sclerosis
VEDOSS: Very early diagnosis of systemic sclerosis

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INTRODUCTION

Systemic sclerosis (SSc) is a multiorgan disease characterised by autoimmunity, fibrosis and vascular damage of the skin and other organs. Its complex pathophysiology is characterised by a dysregulated repair of connective tissue involving microvascular dysfunction and autoimmune phenomena.[1] Among the systemic connective tissue diseases, SSc presents the highest mortality[2], mostly caused by pulmonary arterial hypertension (PAH), interstitial lung disease (ILD) and primary SSc-related cardiomyopathy.[3]

In contrast with the well-recognised and thoroughly studied SSc-associated PAH, the primary cardiac involvement has been an underestimated complication.[4] The pathophysiology underlying these cardiac changes is still unclear, but it is believed that repeated focal ischemia due to coronary microcirculation dysfunction plays an important role.[5] The prevalence of cardiac SSc-related abnormalities varies significantly across studies because of the heterogeneous studied populations and the different cardiovascular diagnostic work-up. Cardiac involvement in the form of pericardial effusion, systolic or diastolic dysfunction with or without heart failure (HF), and arrhythmias, might be present in up to 30-40% of SSc patients.[6] Recently, Tennøe and colleagues showed that 29% of 186 SSc patients had left ventricle diastolic dysfunction, which was independently associated with an almost 4-fold increase in the risk of dying.[7] Diastolic dysfunction is the cardinal and precursor feature of heart failure with preserved ejection fraction (HFpEF), a challenging diagnosis in SSc patients given the multiorgan involvement of this systemic disease. In patients with SSc-associated PAH, the coexistence of HFpEF was associated with increased mortality.[8] Further data on HFpEF in SSc populations is needed.

In the current study, we aimed to examine the prevalence, clinical correlates and prognostic significance of this HF phenotype in a large and unselected SSc population.

METHODS

Study design and population

We performed an observational retrospective study of SSc patients followed at an academic and tertiary hospital (Centro Hospitalar Universitário do Porto, Porto, Portugal) between 1990 and 2019. All data on demographic, clinical, laboratory and echocardiographic parameters were collected by electronic health records review. We evaluated patients with an established diagnosis of SSc according to the current ACR-EULAR classification criteria[9] and patients with very early diagnosis of systemic sclerosis (VEDOSS), with ACR-EULAR score <9, according to Randone et al.[10], who had undergone transthoracic echocardiography. Limited cutaneous (lcSSc) or diffuse cutaneous (dcSSc) scleroderma was defined as previously described by LeRoy et al.[11] Disease duration was defined as the time from diagnosis to the last day of follow-up.

We assessed the first and the last available echocardiogram reports for each patient. LVEF was calculated using either the biplane Simpson method or eyeballing. The patients with an LVEF lower than 50% were excluded from the study. We also excluded patients with a diagnosis of PAH. Dimensions and volumes of cardiac chambers and left ventricular mass were measured according to the current international recommendations.[12]

NT-proBNP was measured using the Roche® NT-proBNP assay. A NT-proBNP measurement >0.125 pg/mL was considered abnormal.[13]

HFpEF was present if the patient had exertional dyspnea and had structural cardiac abnormalities on echocardiography, such as left ventricle hypertrophy (septal or posterior wall thickness more or equal to 11 mm) or left atrial (LA) enlargement (LA with ≥ 38 mm, LA area ≥ 20 cm2 or LA volume ≥ 55 mL).[14] We also evaluated the presence of HFpEF including an abnormal NT-proBNP (> 0.125 pg/mL) in addition to structural cardiac abnormalities on echocardiography and exertional dyspnea in the definition.

All-cause mortality was assessed by eletronic health records review.

This study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local institution's Ethics Committee (N/REF.ª 2019.321).

Statistical analysis

Continuous variables have been expressed as mean ± Standard Deviation (SD). Categorical variables have also been expressed as number and proportion [n (%)]. Comparisons of the study groups were performed using two-sided unpaired or paired t-tests for normally distributed data, and Wilcoxon rank sums test for non-normally distributed data. Fisher's exact test was also applied to compare the proportions. Univariate and multivariate Cox proportional hazards

regression models were employed to assess the unadjusted and adjusted for age associations between HFpEF diagnosis and all-cause mortality. The proportional hazards assumption was assessed by visual inspection of Schoenfeld residuals. All statistical analyses were performed using Stata software, version 12.1 (Stata Corp LP, College Station, TX, USA) and a two-sided P-value < 0.05 was considered to be statistically significant.

RESULTS

Studied population

Of the 214 SSc patients identified, only 188 had an available echocardiogram report, eight were excluded because of PAH (n=5) and LVEF lower than 50% (n=3). The clinical features of the remaining 180 SSc patients are displayed in Table 1. They had a mean age of 54 ± 15 years and 92% were women. Most of the patients had a limited subtype (70%) and there were 31 patients (17%) with very early diagnosis of SSc. Mean disease duration was 11 ± 5 years. Interstitial lung disease (ILD) and Raynaud's phenomenon affected 37% and 96% of the patients, respectively. There were 6% of patients on endothelin receptor antagonists and 33% on immunosuppressant treatment. Regarding the cardiovascular risk profile, the most prevalent modifiable risk factor was dyslipidemia, affecting 47%, followed by hypertension, with 37%. Twelve patients (6%) had a confirmed diagnosis of Ischemic Heart Disease.

Clinical correlates of heart failure with preserved ejection fraction

At baseline, fifty-three patients (29%) of SSc patients had exertional dyspnea, while 42% (n=75) had an abnormal cardiac structure (either LVH or LAE). The prevalence of HFpEF at baseline was 13% (n=24); only half of them (n=12) had a written diagnosis in electronic health records.

Eighty-five per cent (n=153) of the total population had an echocardiographic evaluation during the follow-up (median time between first and second echocardiographic studies was 8.6 [5.7-10.6] years). Among these, 10 additional patients developed exertional dyspnea and an abnormal cardiac structure was diagnosed in 45 patients who had a previous normal echocardiogram. Total prevalence of exertional dyspnea during the follow-up was 35% (n=63) and an abnormal cardiac structure was seen in 67% (n=120) of the patients. During the follow-up, the total prevalence of HFpEF increased to 26% (n=47). Of note, in patients with very early SSc, the prevalence of HFpEF was 13% (n=4).

HFpEF patients were older (60 ± 13 vs 52 ± 15 years, $p<0.001$) and more likely to have ILD (59% vs 28%, $p<0.001$). They had a higher prevalence of atrial fibrillation (11% vs 3%, $p=0.048$) and were more likely to be treated with anticoagulants (24% vs 6%, $p=0.002$). The SSc subtypes were not significantly associated with HFpEF ($p=0.09$).

Of the 155 SSc patients with an available NT-proBNP measurement, 52% (n=80) had abnormally increased plasma levels of this HF-related biomarker, and 25% (n=38) had Heart Failure if we use dyspnea, abnormal echocardiography and increased NT-proBNP to define it. Patients with HFpEF according to this definition were also more likely to be taking diuretics (27% vs 9%, $p=0.049$).

Survival analysis

Over a median follow-up of 10.2 years [5.9-13.5 years], there were 12 deaths (7%) and the mean age at death was 71 ± 10 years. Looking at the prognostic meaning of each criterium of HFpEF, we found that an abnormal NT-proBNP measurement was strongly associated with mortality (HR 12.72, 95% CI: 1.64-98.82, p=0.015). Exertional dyspnea (HR 3.53, 95% CI: 1.06-11.74, p=0.04) was also a predictor of mortality, contrary to an abnormal cardiac structure on echocardiography (HR 2.72, 95% CI: 0.60-12.41, p=0.197), which had a non-significant association with mortality. SSc patients with an HFpEF diagnosis had a death incidence of 13 deaths per 1000 person-years, compared to 4 deaths per 1000 person-years in those without HFpEF. This represents a 2.5-fold increase in the risk of dying (HR 4.26, 95% CI: 1.34-13.5 p=0.01). After adjusting for age, the association estimate still signaled an increased risk but it was not statistically significant (HR 3.13, 95% CI: 0.98-9.95 p=0.05).

DISCUSSION

In a large SSc cohort of 180 patients, we showed a high prevalence of abnormal cardiac structure (67%) and increased plasma levels of NT-proBNP (26%). We found that 15% of these SSc patients fulfilled the diagnostic criteria for HFpEF. These patients were older, had a higher prevalence of ILD and were more likely to have atrial fibrillation. The presence of HFpEF trended to be associated with a worse prognosis, and an abnormal NT-proBNP measurement was strongly associated with mortality.

We observed a prevalence of 26% of HFpEF in SSc patients. This finding is consistent with the current literature, which demonstrates that cardiac involvement is clinically overt in approximately 10 to 30% of patients with SSc.[3,15,16] In this study, 13% of patients with very early subtype of SSc had HFpEF. Few studies have specifically evaluated the primary cardiac involvement in patients with very early diagnosis of SSc, although it has been demonstrated that these patients frequently progresse and eventually fulfill the complete classification criteria of SSc within 5 years of follow-up.[17] The true prevalence of HFpEF in our study may be underestimated for two reasons. First, there was limited echocardiographic data available and therefore we were not able to determine the diastolic function, which lowered the diagnostic sensitivity of the echocardiographic evaluation. Second, since dyspnea was retrospectively assessed, we might have had some degree of information bias and the number of patients with symptoms may have been underreported.

Differentiating primary versus secondary cardiac involvement in SSc patients with HFpEF may be challenging. Primary involvement with diastolic dysfunction may be due to SSc-related focal ischemia from microvascular disease, leading to myocardial fibrosis, and ultimately to a stiff left ventricle.[6] A finding supporting a causal link between SSc and HFpEF development was the higher prevalence of telangiectasias and ILD in patients with HFpEF.[18] It may be hypothesised that the same pathophysiological mechanisms that lead to inflammation, loss-of-function of the small vessels and fibrosis, may be simultaneously damaging the heart. On the other hand, there was an association of HFpEF diagnosis with traditional cardiovascular risk factors, such as increased age, dyslipidemia and atrial fibrillation.[19] The prevalence of cardiovascular comorbidities in HFpEF patients was not as high as in other non-SSc HFpEF cohorts, reporting a prevalence of hypertension of 75%[20] and atrial fibrillation of nearly 30%.[21] It is not clear whether the association between cardiovascular comorbidities and HFpEF is similar to patients without SSc or whether there is a unique interaction between microvascular ischemia in SSc and traditional heart failure risk factors.[19]

In our definition of HFpEF we did not include NT-proBNP. The prevalence of HFpEF including NT-proBNP in the definition (25%) was similar to the prevalence of HFpEF without NT-

proBNP (26%). The association between this HF-related biomarker and all-cause mortality suggests its potential value in clinical practice for both diagnostic and prognostic purposes.

Interestingly, only half of the patients with HFpEF had this diagnosis identified in electronic health records. HFpEF is often unrecognised until late in the course of the disease. This finding illustrates the frequent underdiagnosis of HFpEF and the importance of actively screening for cardiac involvement in SSc.

In our cohort, HFpEF diagnosis signaled a worse prognosis. Previous studies supported the prognostic value of diastolic dysfunction and HFpEF in these populations.[2,3,7,18] In our study, 7% of the patients died over a median follow-up of 10 years. This represents a higher survival rate compared to other SSc cohorts[2,7], which can be explained by the exclusion of patients with PAH who have a poorer prognosis.[3,22,23] Nevertheless, the life expectancy at birth for females in Portugal is 84 years[24], which highlights the increased mortality rate of this cohort (mean age of 71 years old at death) compared to the general population. The low event rate seen in this cohort might have limited the statistical power to detect the prognostic signal of an HFpEF diagnosis. SSc patients with HFpEF have significantly poorer outcomes compared to patients with HFpEF alone.[8] There is scarce data on the causes of death among patients with SSc and HFpEF. According to a study including 5860 SSc patients using the EULAR Scleroderma Trials and Research (EUSTAR) database[3], 55% of total mortality was attributed directly to SSc and 41% to non-SSc causes. Among SSc-related deaths, 35% were related to pulmonary fibrosis, 26% to PAH and 26% to cardiac causes (mainly heart failure and arrhythmias).

This study emphasizes the importance of a timely recognition of the main SSc complications and reassures the presence of HFpEF as a marker of poor prognosis. Further studies on the pathophysiology of the primary cardiac involvement in specific SSc subpopulations are still needed to better understand the impact of this rare autoimmune disease.

LIMITATIONS

The current study has significant limitations that should be considered. First, this study had a retrospective design from a single centre. Second, we had limited echocardiographic data available and, therefore, we were not able to assess the diastolic function in a more detailed way, which may have resulted in underreporting the true prevalence of HFpEF. Finally, although our SSc cohort is quite large, there were few outcome events, which limits our power to detect prognostic associations.

CONCLUSIONS

This study showed a significant prevalence of HFpEF in a large SSc cohort. HFpEF was associated with cardiovascular risk factors and atrial fibrillation, as well as SSc-related lung involvement. The presence of HFpEF and an increased NT-proBNP value were associated with a worse prognosis.

APPENDIX

Table I. Clinical characteristics of the studied patients. Abbreviations: SSc, systemic sclerosis; HF, heart failure; ACA, anti-centrome antibodies; DLCO, diffusing capacity of the lung for carbon monoxide; DLCO/SB, single breath; DLCO/VA, total alveolar volume; FVC, forced vital capacity; FEV1, volume of air forcibly expired in the first second; BMI, body mass index; Hg, hemoglobin; ACEI/ARB, angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker; AAS, acetylsalicylic acid (aspirin).

Table I. Clinical characteristics of the studied patients

Characteristics	Total (n=180)	No HFpEF n = 133	HFpEF n = 47	*p*-value
Demographic Characteristics				
Age, y	54.2 ± 14.6	52.0 ± 14.6	60.0 ± 12.9	0.001
Male, n (%)	14 (7.8%)	10 (7.5%)	4 (8.5%)	0.83
Disease Duration,y	11.3 ± 4.8	11.2 ± 4.8	11.5 ± 5.0	0.66
SSc subtype				
Difuse	23 (12.8%)	14 (10.5%)	9 (19.1%)	
Limited	126 (70.0%)	92 (69.2%)	34 (72.3%)	0.09
Very early	31 (17.2%)	27 (20.3%)	4 (8.5%)	
Clinical and Serological Characteristics				
Telangiectasia	93 (51.66%)	66 (49.6%)	27 (57.4%)	0.36
ACA	106 (58.9%)	77 (57.9%)	29 (61.7%)	0.65
Raynaud's phenomenon	172 (95.6%)	128 (96.2%)	44 (93.6%)	0.45
Interstitial Lung Disease (ILD)				
Mild, n (%)	46 (28.2%)	29 (24.8%)	17 (37.0%)	<0.001
Severe, n (%)	14 (8.6%)	4 (3.4%)	10 (21.7%)	
Pulmonary function test				
DLCO/SB	76.8 ± 17.3	79.7 ± 17.1	69.8 ± 14.7	<0.001
DLCO/VA	79.8 ± 13.2	80.0 ± 13.3	79.6 ± 12.0	0.86
FEV1/FVC	81.8 ± 9.2	82.6 ± 9.2	79.6 ± 8.7	0.06
Hypertension, n (%)	66 (36.7%)	45 (33.8%)	21 (44.7%)	0.18
Dyslipidemia, n (%)	85 (47.2%)	60 (45.1%)	25 (53.2%)	0.34
BMI ≥ 30 kg/m2, n (%)	12 (17.9%)	9 (17.0%)	3 (23.0%)	0.59
Diabetes, n (%)	18 (10.0%)	11 (8.3%)	7 (14.9%)	0.19
Smoking Status				
Never smoked, n (%)	151 (83.9%)	109 (82.0%)	42 (89.4%)	
Current smoker, n (%)	13 (7.2%)	10 (7.5%)	3 (6.4%)	0.40
Past smoker, n (%)	16 (8.9%)	14 (10.5%)	2 (4.3%)	
Ischemic Heart Diease, n (%)	12 (6.7%)	8 (6.0%)	4 (8.5%)	0.56
Atrial Fibrillation				
Permanent, n (%)	8 (4.4%)	3 (2.3%)	5 (10.6%)	0.048
Paroxistic, n (%)	1 (0.6%)	1 (0.8%)	0 (0.0%)	
Hg, g/dl	13.2 ± 1.3	13.2 ± 1.3	13.2 ± 1.4	0.72
Creatinine, mg/dl	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.74
Chronic Medication				
ACEI/ARB, n (%)	52 (29.1%)	37 (27.8%)	15 (32.6%)	0.54
B-blocker, n (%)	18 (10.1%)	11 (8.3%)	7 (15.2%)	0.18
Furosemide, n (%)	20 (11.2%)	12 (9.0%)	8 (17.4%)	0.12
Statin, n (%)	65 (36.3%)	47 (35.3%)	18 (39.1%)	0.64
AAS, n (%)	42 (23.5%)	29 (21.8%)	13 (28.3%)	0.37
Anticoagulant, n (%)	18 (10.0%)	9 (6.8%)	9 (19.1%)	0.02
Endothelin receptor antagonist, n (%)	11 (6.1%)	9 (6.8%)	2 (4.3%)	0.56
Immunosuppressive Drugs, n (%)	59 (33.0%)	46 (34.6%)	13 (28.3%)	0.43

Table II. Supplemental Table I. Characteristics of the studied population according to HFpEF status including NT-proBNP in the definition. Abbreviations: SSc, systemic sclerosis; HF, heart failure; BNP, brain natriuretic peptide; ACA, anti-centrome antibody; DLCO, diffusing capacity of the lung for carbon monoxide; DLCO/SB, single breath; DLCO/VA, total alveolar volume; FVC, forced vital capacity; FEV1, volume of air forcibly expired in the first second; BMI, body mass index; Hg, Hemoglobin; ACEI/ARB, angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker; AAS, acetylsalicylic acid (aspirin).

Supplemental Table I. Characteristics of the studied population according to HFpEF status including NT-proBNP in the definition

Characteristics	**No HFpEF n = 117**	**HFpEF n = 38**	***p*-value**
Demographic Characteristics			
Age, y	51.3 ± 14.1	62.5 ± 11.4	< 0.001
Male, n (%)	9 (7.7%)	4 (10.5%)	0.58
Disease Duration,y	11.6 ± 4.8	11.1 ± 4.4	0.58
SSc subtype			
Difuse	17 (14.5%)	5 (13.2%)	
Limited	79 (67.5%)	30 (78.9%)	0.29
Very early	21 (17.9%)	3 (7.9%)	
Clinical and Serological Characteristics			
Telangiectasia	53.0 (45.3%)	25 (65.8%)	0.03
ACA	69 (59.0%)	23 (60.5%)	0.87
Raynaud's phenomenon	113 (96.6%)	37 (97.4%)	0.81
Interstitial Lung Disease (ILD)			
Mild, n (%)	25 (23.6%)	14 (37.8%)	0.001
Severe, n (%)	6 (5.7%)	8 (21.6%)	
Pulmonary function test			
DLCO/SB	79.0 ± 17.8	69.0 ± 15.5	0.003
DLCO/VA	79.8 ± 13.7	78.7 ± 12.3	0.68
FEV1/FVC	81.9 ± 8.2	79.2 ± 9.5	0.10
Hypertension, n (%)	38 (32.5%)	19 (50.0%)	0.05
Dyslipidemia, n (%)	52 (44.4%)	24 (63.2%)	0.045
BMI ≥ 30 kg/m2, n (%)	9 (20.0%)	2 (20.0%)	1.00
Diabetes, n (%)	11 (9.4%)	6 (15.8%)	0.27
Smoking Status			
Never smoked, n (%)	95 (81.2%)	33 (86.8%)	
Current smoker, n (%)	9 (7.7%)	3 (7.9%)	0.57
Past smoker, n (%)	13 (11.1%)	2 (5.3%)	
Ischemic Heart Diease, n (%)	8 (6.8%)	4 (10.5%)	0.46
Atrial Fibrillation			
Permanent, n (%)	3 (2.6%)	5 (13.2%)	0.03
Paroxistic, n (%)	1 (0.9%)	0 (0.0%)	
Hg, g/dl	13.3 ± 1.2	13.0 ± 1.5	0.24
Creatinine, mg/dl	0.70 ± 0.20	0.70 ± 0.20	0.44
Chronic Medication			
ACEI/ARB, n (%)	33 (28.2%)	13 (35.1%)	0.42
B-blocker, n (%)	9 (7.7%)	6 (16.2%)	0.13
Furosemide, n (%)	11 (9.4%)	8 (21.6%)	0.049
Statin, n (%)	41 (35.0%)	17 (45.9%)	0.23
AAS, n (%)	27 (23.1%)	13 (35.1%)	0.14
Anticoagulant, n (%)	7 (6.0%)	9 (23.7%)	0.002
Endothelin receptor antagonist, n (%)	9 (7.7%)	2 (5.4%)	0.64
Immunosuppressive Drugs, n (%)	43 (36.8%)	12 (32.4%)	0.63

REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017 Oct 7;390(10103):1685–99.
2. Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum. 2014 Oct;44(2):208–19.
3. 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 Oct;69(10):1809–15.
4. Bissell L-A, Anderson M, Burgess M, et al. Consensus best practice pathway of the UK Systemic Sclerosis Study group: management of cardiac disease in systemic sclerosis. Rheumatology (Oxford). 2017 01;56(6):912–21.
5. Kahan A, Allanore Y. Primary myocardial involvement in systemic sclerosis. Rheumatology (Oxford). 2006 Oct;45 Suppl 4:iv14-17.
6. Bissell L-A, Md Yusof MY, Buch MH. Primary myocardial disease in scleroderma-a comprehensive review of the literature to inform the UK Systemic Sclerosis Study Group cardiac working group. Rheumatology (Oxford). 2017 01;56(6):882–95.
7. Tennøe AH, Murbræch K, Andreassen JC, et al. Left Ventricular Diastolic Dysfunction Predicts Mortality in Patients With Systemic Sclerosis. J Am Coll Cardiol. 2018 09;72(15):1804–13.
8. Bourji KI, Kelemen BW, Mathai SC, et al. Poor survival in patients with scleroderma and pulmonary hypertension due to heart failure with preserved ejection fraction. Pulm Circ. 2017 Jun;7(2):409–20.
9. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013 Nov;65(11):2737–47.
10. Belando-Randone S, Matucci-Cerinic M. Very Early Systemic Sclerosis and Pre-Systemic Sclerosis: Definition, Recognition,Clinical Relevance and Future Directions. Curr Rheumatol Rep 2017 19:65
11. LeRoy EC, Black C,Fleischmajer R, et al. Scleroderma(Systemic Sclerosis): Classification, Subsets and Pathogenesis. J Rheumatol. 1988; 15(2):202-5
12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015 Jan;28(1):1-39.e14.
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891–975.
14. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. JACC Heart Fail. 2017;5(7):471–82.
15. Desai CS, Lee DC, Shah SJ. Systemic sclerosis and the heart: current diagnosis and management. Curr Opin Rheumatol. 2011 Nov;23(6):545–54.
16. Parks JL, Taylor MH, Parks LP, Silver RM. Systemic sclerosis and the heart. Rheum Dis Clin North Am. 2014 Feb;40(1):87–102.
17. Bellando-Randone S, Lepri G, Huscher D, et al.Predictors to Develop Definite Systemic Sclerosis (SSc): Results from an International Multicentre Study on Very Early Diagnosis of Systemic Sclerosis (VEDOSS) [Internet]. ACR Meeting Abstracts. [cited 2020 Jun 12]. Available from: https://acrabstracts.org/abstract/predictors-to-develop-definite-systemic-sclerosis-ssc-results-from-an-international-multicentre-study-on-very-early-diagnosis-of-systemic-sclerosis-vedoss/
18. Ioannidis JPA, Vlachoyiannopoulos PG, Haidich A-B, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med. 2005 Jan;118(1):2–10.

19. Hinchcliff M, Desai CS, Varga J, Shah SJ. Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis. Clin Exp Rheumatol. 2012 Apr;30(2 Suppl 71):S30-37.
20. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999 Jun;33(7):1948–55.
21. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. Circulation. 2013 Sep 3;128(10):1085–93.
22. Lefèvre G, Dauchet L, Hachulla E, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum. 2013 Sep;65(9):2412–23.
23. Fisher MR, Mathai SC, Champion HC, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum. 2006 Sep;54(9):3043–50.
24. WHO | Portugal [Internet]. WHO. World Health Organization; [cited 2020 Mar 21]. Available from: http://www.who.int/countries/prt/en/