

LEFT VENTRICULAR DIASTOLIC DYSFUNCTION PREDICTS MORTALITY IN A LARGE UNSELECTED SYSTEMIC SCLEROSIS (SSC) COHORT

Diastolic dysfunction in systemic sclerosis

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Abstract:

Background: Primary cardiac affection is common and a major cause of death in systemic sclerosis (SSc), but there are knowledge gaps regarding the impact of cardiac dysfunction on mortality.

Objectives: Evaluate diastolic function in a large unselected SSc-cohort and assess the impact of diastolic dysfunction (DD) on mortality.

Methods: SSc patients followed prospectively at the Oslo University Hospital from 2003 to 2016 with available echocardiographies and matched controls were included. DD was assessed by echocardiography according to the 2016 ASE/EACVI guidelines. Pulmonary hypertension (PH) was diagnosed by right heart catheterization. Vital status was available for all patients. Cox regression analyses with hazards ratios (HR) were conducted.

Results: We assessed diastolic function in 275 SSc patients at baseline and in 186 at follow-up. At baseline, 46 of the 275 SSc patients (17 %) were diagnosed with DD and 195 (71%) had normal diastolic function. After a median follow-up of 3.4 years (IQR 1.6-6.2), the proportion of DD increased from 17% to 29 %. During follow-up, 57% patients with DD at baseline died, compared to 13% patients with normal diastolic function. At baseline, 86 patients had performed right heart catheterization, and 43 were diagnosed with PH; of these 60% deceased. In multivariable Cox regression analyses, DD was a stronger predictor of death (HR 3.7, 95%CI 1.69 – 8.14, c-index 0.89) than PH (HR 2.0, 95%CI 1.1-3.9, c-index 0.84).

Conclusion: DD is frequent in SSc; and the presence of DD is associated with high mortality. DD exceeds PH with respect to predicting mortality.

Condensed abstract:

Systemic sclerosis presents high mortality, and pulmonary hypertension (PH) is traditionally regarded as the major risk factor for death. Diastolic dysfunction is a recognized complication of SSc, but there is limited knowledge on its impact on mortality. In the large unselected Oslo University Hospital SSc cohort, we found that diastolic dysfunction was frequent, and strongly associated with mortality. After a median observation of 2.5 years, mortality in patients with diastolic dysfunction was 57%, compared to 13% in patients with normal diastolic function, and 60% in PH. However, diastolic dysfunction exceeded PH as a predicting factor for mortality in multivariable analyses.

Keywords:

Systemic sclerosis, diastolic dysfunction, mortality, echocardiography.

Abbreviations:

CI= Confidence interval

DD = Diastolic dysfunction

HFpEF= Heart failure with preserved ejection fraction

HR= Hazard ratio

IHD= Ischemic heart disease

ILD= Interstitial lung disease

LAVI= Left atrial volume index

LVEF= Left ventricular ejection fraction

NT-proBNP= N-terminal prohormone of brain natriuretic peptide

OR= Odds ratio

PH = Pulmonary hypertension

SSc = Systemic sclerosis/scleroderma.

TRV= Tricuspid regurgitant maximum velocity

Introduction:

Systemic sclerosis (SSc) is a severe and progressive, but heterogeneous systemic connective tissue disease characterized by vasculopathy, dysregulation of the immune system and extensive fibrous tissue formation. Among the systemic connective tissue diseases, SSc presents the highest mortality (1).

Estimates from the European Scleroderma Trials and Research Group database indicate that the excessive mortality in SSc is mainly due to pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), and disease-related cardiac causes; with cardiac causes accounting for 26% of the mortality defined as SSc-related (2).

Previous autopsy studies indicate that cardiac fibrosis is highly common in SSc (3, 4). Mechanistically, it appears that disease-related loss-of-function of small coronary arteries and arterioles, leads to ischemia and reperfusion injury, driving cardiac fibrotic tissue formation (5, 6). Most cardiac affection is assumed to develop over the first years of the disease (7). Yet, most previous studies on cardiac function in SSc have not included serial measurements, making it challenging to elucidate how cardiac dysfunction evolves from baseline and onwards (8-13).

Diastolic dysfunction (DD) is regarded a precursor of heart failure with preserved ejection fraction (HFpEF) (14). Prior studies applying different combinations of echo-parameters have reported reduced diastolic function in 18-62% of SSc cases (8, 10, 15), and DD assessed by the single parameter e' , was reported a predictor of mortality in two smaller SSc cohorts (9, 15).

To simplify and standardize the evaluation of diastolic function, the American Society of Echocardiography and the European Association of Cardiovascular Imaging established new guidelines in 2016 (16). To our knowledge, there are to date no studies estimating DD by these guidelines in a large and unselected SSc cohort.

The present study aimed to: (a) evaluate the frequency of DD at baseline and follow-up in a large unselected SSc-cohort, and (b) determine the impact of diastolic function on mortality, applying the new criteria for diastolic function.

Methods:

Study cohort

All SSc-patients followed at the Oslo University Hospital are included in the prospective Oslo SSc cohort. Patients are followed on an annual basis by a rheumatologist, and data on demographic, clinical, laboratory and imaging parameters are registered. Echocardiographies are performed routinely on all SSc patients in order to detect occult pulmonary hypertension (PH).

The present study involved patients registered between 2003 and 2016 with the following inclusion criteria: (1) fulfillment of the 2013 European League Against Rheumatism/American College of Rheumatology criteria (17), or the 1980 criteria (18), for SSc and (2) at least one available echocardiography with adequate image quality. This study complied with the Declaration of Helsinki. The Regional Committee of Health and Medical Research Ethics in South-East Norway approved the research protocol (No.2017/1815). Informed consent was obtained from all included subjects.

Clinical data

Data on demographics, date of diagnosis, and clinical presentation (including SSc subtype, modified Rodnan skin score, digital ulcers, ILD and PH) were collected from the Oslo SSc cohort and from electronic patient journals. SSc subsets were evaluated as limited cutaneous SSc and diffuse cutaneous SSc based on extent of skin involvement (19). ILD was defined as the presence of > 10% pulmonary fibrosis on high resolution computer tomography or two consecutive measurements of forced vital capacity <70% in the absence of imaging (20, 21).

Right heart catheterization was performed on patients suspected of PH, based on echocardiography findings, clinical suspicion or the DETECT algorithm (22). PH was defined as a mean pulmonary arterial pressure ≥ 25 mmHg according to the European Society of Cardiology guidelines (23). Comparing the impact of primary cardiac and pulmonary disease on mortality, we defined PH as pre-capillary PH, excluding post-capillary PH from analyses. Pre-capillary PH was defined PH with a pulmonary capillary wedge pressure < 15 mmHg (23). PAH and PH-ILD were defined as pre-capillary PH in absence or presence of ILD, respectively (24). Serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) values at baseline were collected. Disease duration was defined as time from diagnosis to baseline echocardiography, and the observation period as time from baseline echocardiography to date of death or study end (April 2017). Systemic hypertension was defined as the composite of both a hypertension diagnosis by the international classification of diseases-10 code registered at Oslo University Hospital and a systolic blood pressure ≥ 140 mmHg at time of baseline echocardiography. Data on ischemic heart disease (IHD), heart failure and atrial fibrillation was collected from electronic patient journals. At study end, vital status was available for all patients.

Control group

In total, 65 controls were collected from the Nord-Trøndelag Health Study (25). This population based study contained echocardiographies from 1,266 participants without recognized systemic hypertension, cardiovascular disease or diabetes mellitus. Controls were matched to the SSc patients with respect to age, sex, systolic blood pressure and body mass index at time of baseline echocardiography.

Echocardiographic analyses

The earliest accessible echocardiography from each patient was considered baseline echocardiography, and the most recent echocardiography was considered follow-up

echocardiography. All examinations were performed at a single center, Oslo University Hospital, Rikshospitalet. Ultrasound recordings were obtained using GE Vivid 7 or Vivid E9 (GE Vingmed Ultrasound, Horten, Norway). Patients were examined in the left decubitus position and software analyses were performed using EchoPAC, version 201. All examinations were reanalyzed for the present study between September 2016 and July 2017 by the same investigator (A.H.T.), blinded for patient clinical status. To assure adequate inter-observer variability, 43 examinations were analyzed by a second observer (J.C.A.), and 19 examinations were reanalyzed in order to assure adequate intra-observer variability.

Diastolic function was assessed measuring transmitral flow pattern by pulsed Doppler, tissue Doppler displacement of the septal mitral annulus during early diastole (e' and E/e'), body surface indexed left atrial volumes by the biplane area length method (LAVI) and tricuspid regurgitant maximum velocity (TRV) by continuous Doppler (16). The 2016 guidelines on diastolic function were applied to evaluate diastolic function as a composite outcome (16). All four parameters were utilized for evaluation of diastolic function in the entire cohort; including TRV in patients with pre-capillary PH and LAVI in patients with mitral regurgitation. DD was defined as abnormality in more than 50% of the available parameters, while abnormality in less than 50% indicated normal diastolic function. In cases of 50% abnormal parameters, status was considered inconclusive. We applied these guidelines on all patients with ≥ 2 evaluable parameters. In order to compare patients clearly segregated by diastolic function, patients with inconclusive diastolic function were excluded from analyses on mortality. Patients with normal or inconclusive diastolic function at baseline, and a DD diagnosis at the follow-up echocardiography, were defined new onset DD.

DD was segregated into three severity grades; grade I, II and III, using early and late transmitral flow velocities and number of abnormal diastolic parameters, as recommended by the guidelines (16).

Left ventricular systolic function was evaluated by ejection fraction, using the Simpson biplane method, and by global longitudinal strain, averaging values from apical long axis, four- and two-chamber views (26). Systolic right sided parameters as tricuspid annular plane systolic excursion, fractional area change and right ventricular free wall longitudinal strain, right ventricular dimensions and right atrial area were all evaluated in the four-chamber view. Mitral regurgitation was categorized as mild, moderate or severe. Pericardial effusion was categorized as mild (<5 mm), moderate (5-15 mm) or severe (≥ 15 mm).

Statistical analyses

Statistical analyses were performed using SPSS, version 23 and STATA, version 14. Paired and independent t-tests, non-parametric tests and chi-square tests were applied as appropriate for continuous and categorical data, respectively. For analyzing correlations, Pearson or Spearman coefficients were applied as appropriate. Parameters with more than two variables were analysed with one-way ANOVA, and post hoc tests were applied. Logistic regressions with odds ratios (OR) and 95% confidence intervals were applied to investigate associations between DD and clinical characteristics. Cox regressions with hazards ratios (HR) and 95% confidence intervals were applied for prediction of mortality. Clinical, laboratory and echocardiographic parameters of relevance were assessed. Only factors presenting significance levels <20% in univariable analyses, along with variables of clinical known importance, were allowed for inclusion in multivariable Cox regression analyses. A manual backward stepwise elimination procedure was performed to identify independent risk factors for mortality. In order to determine independent predictor variables, and control for confounding from other parameters of the multivariable models, parameters with significance levels >0.05 (27) were eliminated from the models. Multiple regression analyses were preceded by estimation of correlation between the respective parameters. In order to avoid multicollinearity, parameters presenting high correlations were not included in common

models. Multivariable Cox models were discriminated by the c-index (values >0.7 were considered acceptable). Cumulative survival rates were computed by the Kaplan-Meier method and significance was tested with the log-rank test.

Results:

Study cohort

We included 333 consecutive SSc patients with baseline echocardiographies available for analyses. Mean age was 58 ± 14 years, 83% were female and 71% had limited cutaneous SSc. Median disease duration at baseline echocardiography was 1.6 years (0.3-7.4 inter quartile range) (Table 1). Data on IHD, systemic hypertension, right heart catheterization, heart failure, PH and medication are presented in Table 1. As detailed later, a follow-up echocardiography was available for analyses in 207 of the 333 patients (62%) with baseline echocardiographies.

Systolic function at baseline

Left ventricular systolic function, measured by LVEF, was reduced in SSc patients compared to controls (Table 2). A mid-range LVEF of 40-49% (28) was present in 21 patients (8%) of the entire cohort and nine patients (3%) had LVEF <40%. All controls had LVEF >50%.

Left ventricular diastolic function at baseline

At least two of the required parameters for DD were available and evaluated in 275/333 of the cohort patients (83%), and 241 patients presented a conclusive either normal diastolic function or DD (Tables 1 and 2). There were no differences between these 275 patients and the 58 patients who did not have evaluable diastolic function with respect to age at echocardiography, sex, SSc subtype, disease duration, systemic hypertension, IHD, body mass index, PH or ILD. We did, however, find that mortality was higher in the 58 patients

with non-evaluable diastolic function than in the 275 with evaluable function (55% versus 24%, $p<0.001$) and they had numerically lower mean LVEF (55% vs 58%, $p=0.075$).

At baseline, 46 of the 275 patients (17%) with evaluable diastolic function fulfilled the criteria for DD, 34 (12%) had an inconclusive evaluation and 195 (71%) had normal diastolic function. Of the 46 patients with DD, 41 were possible to categorize; 15% had DD grade I, 54% grade II and 5% grade III; the last 27% were inconclusive between grade I and II.

Patients with DD were older at baseline, had higher accumulated frequencies of systemic hypertension, IHD and PH at study end, compared to patients with normal diastolic function. DD patients also exhibited reduced right ventricular function (Table 2). There were no differences between the groups stratified by diastolic function regarding sex, SSc subset, LVEF, body mass index or ILD (Table 1).

We found that the 34 patients with inconclusive diastolic function differed from the 195 patients with normal diastolic function regarding age at baseline (63 ± 11 versus 54 ± 13 years, $p<0.001$), frequency of hypertension (24% versus 8%, $p=0.045$), PH (35% versus 15%, $p=0.031$) and all-cause mortality (44% versus 13%, $p=0.001$), but there were no differences with respect to sex, disease duration, IHD, ILD, body mass index or LVEF.

Among the controls, four individuals (6%) fulfilled the DD criteria. In terms of the diastolic parameters e' , E/e' and left atrial area, we found no difference between controls and SSc patients with normal diastolic function, while SSc patients with DD differed from the controls (Table 2). Patients presented a higher rate of pathological TRV.

Factors associated with diastolic dysfunction

In univariable logistic regression, baseline DD was associated with age at baseline, systemic hypertension, calcinosis, PH, New York Heart Association functional class, six minute walk test, NT-proBNP and IHD. In multivariable logistic regression, adjusted for gender, baseline DD was associated with age at baseline (OR 1.09, 95%CI 1.03-1.15,

p=0.004), NT-proBNP (OR 1.01, 95%CI 1.01-1.02, p=0.001), PH (OR 3.03, 95%CI 1.01-9.17, p=0.049) and calcinosis (OR 5.86, 95%CI 1.74-19.71, p=0.004).

Diastolic dysfunction and mortality

In total, 98 of the 333 patients (29%) died during the observation period. The 5- and 10 year survival rates for the entire cohort were 76% and 54% respectively (Figure 2). Among patients with PH at baseline, 26/43 (60%) were dead at study end. Stratification by baseline diastolic function revealed higher death rates in patients with DD (26/46; 57%) than in patients with normal diastolic function, (25/195; 13%; p<0.001). The 26 deceased DD patients did not differ from the 20 DD survivors regarding LVEF or observation period, but showed a numerical, non-significant *lower* age at baseline compared to DD-survivors (66 vs 69 years, p=0.293). Six of the DD patients had moderate or severe mitral regurgitation, of which one died during the observation period.

Pharmacological treatment

DD patients had higher frequency of cumulative cardiovascular medication than patients with normal diastolic function (Table 1). However, no significant differences were found between subsets of deceased patients from the two groups.

Risk factors for mortality in the study cohort

In univariable Cox regression analysis, mortality was predicted by higher age at baseline echocardiography, presence of DD, PH, ILD, calcinosis, pericardial effusion and tendon friction rubs, absence of anti-centromere antibodies, lower diffusing capacity of the lung for carbon monoxide and LVEF, higher modified Rodnan skin score, creatinine and NT-proBNP, abnormal left sided diastolic parameters, abnormal right sided systolic parameters and larger right atrial area. In the final multivariable regression model, diastolic dysfunction was an independent predictor of mortality (Table 3).

Predicting mortality in SSc-PH

TRV approximates pressure of the pulmonary arteries during systole and is considered a valid marker of left atrial pressure in patients without pulmonary vascular disease. By excluding TRV from the DD algorithm in patients with established PH, DD remained a highly significant predictor of mortality, increasing c-index to 0.90 in multivariable Cox regression. PH independently predicted mortality (HR 2.0 (95%CI 1.1-3.9), p=0.039) in a model including age, sex, modified Rodnan skin score and NT-proBNP (c-index 0.84).

Longitudinal assessment of Diastolic dysfunction

Among patients with follow-up echocardiographies available, 186 (90%) had an echocardiography that was evaluable for diastolic function. Median time from baseline to follow-up echo was 3.4 years (inter quartile range 1.6-6.2). Individual DD parameter analyses showed that the frequencies of patients with pathological e', LAVI, TRV and E/e' was higher at follow-up than at baseline (Table 4).

DD was diagnosed in 54 patients (29%) at follow-up. Patients with new onset DD at follow-up showed a trend to higher mortality (8/26; 31%) than patients with normal diastolic function at follow-up (12/106; 11%; p=0.055.)

Inter- and intraobserver variability

Inter- and intraclass correlations coefficients for e', E/e', and left atrial area in four chamber-view were 0.98 and 0.97, 0.98 and 0.99, 0.94 and 0.94, respectively. Interclass correlation coefficient for TRV was 0.99.

Discussion:

Previous studies, mostly investigating smaller cohorts, indicated high frequencies of reduced diastolic function in SSc, however not applying newly established DD definitions (8, 9, 11, 15, 29). Here, we show in a large and unselected SSc cohort that DD, defined by the

2016 echocardiographic guidelines on diastolic function, increases in frequency and severity during the disease course; and has a high impact on mortality in SSc patients which appears to exceed that of pre-capillary PH.

Prevalence of diastolic dysfunction

We consider the current SSc study cohort to be largely unselected, as most patients in South East Norway (with a population of 2.7 million) are referred to Oslo University Hospital for an inter-disciplinary evaluation. In this cohort, we found a 17% cumulative incidence of DD at baseline and 29% at follow-up after a median follow-up time of 3.4 years. These DD frequencies are in the lower range of previous reports and may represent actual divergence from other cohorts. It may, however, also be due to the stricter definitions of DD applied, short disease duration at baseline, and that many earlier studies were from tertiary centers, potentially excluding patients with milder disease.

Diastolic dysfunction, cardiovascular risk factors and mortality

In 2011, Hinchcliff et al showed that the diastolic parameter e' was predictive for mortality in SSc patients (9); this was further supported by Faludi et al in 2014 (15). While e' is a marker of left ventricular relaxation, evaluation of diastolic function is today recommended to also rely on parameters of ventricular filling pressure (LAVI, TRV and E/e') (16).

The DD group in our cohort was 13 years older at baseline than patients with normal diastolic function, and a higher mortality would be expected. However, in Norway, female life expectancy exceeds 84 years (30). This illustrates that the mortality rate in our cohort is very high considering their median age of 67 years, and a median follow-up of 2.5 years. Finally, in the final Cox regression model, both age and DD predicted mortality independently. If the effect on mortality from diastolic dysfunction was due to higher age, we would expect age to

remain an independent predictor, while diastolic dysfunction would lose significance.

However, in the model, both remained significant predictors.

Creatinine was not permitted for inclusion in a common multivariable model with NT-proBNP due to high correlation. However, replacing NT-proBNP with creatinine in the multivariable mode, creatinine failed to predict mortality independently, adjusted for other parameters of the model.

Among DD patients, 13/46 (28 %) were registered with a code of IHD at some time during the study period. Five of these 13 patients died during the study period. The DD subset with IHD presented a lower mortality (38 %, n=13) than the rest of the DD group (64 %, n=33). The DD group presented a higher amount of IHD compared to the group with normal diastolic function. However, in Cox regression, IHD failed to predict mortality, even at a univariable level. This supports the notion that mortality in SSc is highly dominated by other causes, outweighing the impact of IHD.

The current study design does not allow for assessment of causality between DD and death. Patients might die due to other SSc-complications, or even non-SSc related events, but DD seems to be either a primary or a contributing cause of death.

DD, a primary cardiomyopathy or due to right sided dysfunction?

Patients with idiopathic pulmonary arterial hypertension are known to present a high prevalence of DD, associated with worse hemodynamics and outcome (31). Elevated right ventricular pressure may bulge the interventricular septum towards the left side (32, 33), impairing left ventricular filling (34). It is therefore not surprising that many PH patients in our cohort also show a high co-existence of DD. In our study, 52% of patients with baseline DD developed PH during the disease course. Surprisingly, DD exceeded PH in respect of predicting mortality. Although effective treatment of DD is awaited, our study proposes that patients who display DD may require a closer follow-up.

Traditionally, few SSc-PH cases are thought to arise from left-sided heart disease (35), and our cohort included only 14 patients (4%) with post-capillary PH. However, a Canadian study showed that although the majority of SSc-PH patients initially were considered pre-capillary PH, fluid-challenge revealed occult left-heart-disease, making post-capillary the dominant PH group (36). It is possible that some patients diagnosed with pre-capillary PH in fact may suffer from post-capillary PH secondary to DD (37). Further studies are warranted to clarify this important issue.

HFpEF in SSc, an underestimated complication?

DD is the hallmark of HFpEF (38), which appears to have equal morbidity and mortality as heart failure with reduced ejection fraction (39). Data on HFpEF in SSc are limited, but Bourji et al showed a twofold increased risk of death in SSc patients with combined PH and HFpEF compared with isolated SSc-pulmonary arterial hypertension (40). HFpEF is more difficult to disclose than heart failure with reduced ejection fraction as patients show normal ejection fractions and levels of natriuretic peptides are significantly lower (41). Patients suffering from heart failure may present lower range NT-proBNP (42) and natriuretic peptide levels have been reported to be especially low in patients of female sex and lower age (43); both features common in SSc patients. Heart failure symptoms in SSc may resemble pulmonary complications; and dyspnea related to heart failure may be misinterpreted as ILD or PH, leaving HFpEF underdiagnosed in SSc. Further studies on the impact and treatment of these conditions in SSc are therefore in demand.

Limitations

A potential limitation is that the echocardiographies were re-evaluated for the present study and not originally recorded with respect to the present guidelines for diastolic assessment. Hence, 58 cohort patients were excluded because they had inadequate images for baseline diastolic evaluation. This group accounted for 32 of deceased patients and was not

utilized in analyses on DD and mortality. As the groups mostly showed resemblance, we consider our analyses generalizable for the entire cohort.

Secondly, apart from NT-proBNP values, our cohort did not include data on HFpEF. Such data would have made it possible to differentiate between symptomatic and asymptomatic diastolic dysfunction in the predictive analyses.

When evaluating PH as a predictor variable, complete data on invasive measurements of all patients would be ideal. We still consider right heart catheterization of 51 % of the cohort a high percentage.

Lastly, although our cohort is fairly large, the number of outcomes in categories as DD and new onset DD were fairly few. This limits the ability of drawing conclusions on predicting new onset DD and prognosis.

Conclusion:

Our study, applying the 2016 echocardiographic guidelines for DD on a large unselected cohort, implies a high frequency of DD in SSc, and a more detrimental impact on mortality than assumed from previous reports. DD strongly predicts mortality, even exceeding the role of pre-capillary PH.

Perspectives:

Competency in Medical Knowledge: Patients with systemic sclerosis (SSc) and diastolic dysfunction (DD) show a significantly decreased survival. Among clinical and echocardiographic factors, DD seems to be a major predictor of mortality.

Competency in Patient Care: The physician must appreciate the possibility of diastolic dysfunction, and its potential impact, even in SSc-patients suffering from pulmonary complications.

Translational outlook 1: Disclosing HFpEF in SSc is challenging as other causes of dyspnea are frequent in SSc. Further studies are warranted in order to evaluate correlation between DD and HFpEF, and the burden of HFpEF in SSc.

Translational outlook 2: Despite being considered as one of the leading causes of SSc-related deaths, cardiac dysfunction is in lack of specific treatment. Further therapeutic studies are needed.

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Figure legends:

Central illustration: Distribution of diastolic function in systemic sclerosis.

Boxes in green, yellow, orange and grey show SSc-groups segregated by diastolic function and associated number of deceased patients (in black). Arrows from left to right denote number of patients from each group presenting diastolic dysfunction at follow-up.

DD, diastolic dysfunction; SSc, systemic sclerosis.

Figure 2: SSc-cohort survival, segregated by diastolic function at baseline echocardiography.

Kaplan-Meier plot with confidence intervals on survival of SSc-patients segregated by diastolic function.

Figure 3: SSc-cohort survival, segregated by diastolic function at follow-up echocardiography.

Kaplan-Meier plot with confidence intervals on survival of SSc-patients segregated by diastolic function.

Table 1: Clinical and demographic parameters of the entire SSc cohort, and stratified by diastolic dysfunction.

	Total cohort (n=333)	Diastolic dysfunction (n=46)	Normal diastolic function (n=195)	p-value
Age at baseline, years	58 (14)	67 (11)	54 (13)	<0.01
Disease duration at baseline, years	1.6 (0.3-7.4)	1.8 (0.3-10.3)	1.5 (0.3-5.6)	0.43
Observation period, years	4.9 (2.1-7.2)	2.6 (1.1-6.2)	5.3 (2.6-7.4)	<0.01
Female, n (%)	275 (83)	37 (80)	166 (85)	0.43
lcSSc, n (%)	237 (71)	36 (78)	134 (69)	0.22
ACA, n (%)	170 (51)	28 (61)	100 (51)	0.24
ATA, n (%)	57 (17)	4 (9)	38 (19)	0.08
mRSS	6.0 (3.0-14.0)	6.5 (3.3-15)	5.0 (2.0-13.0)	0.47
Digital ulcers, n (%)	140 (42)	16 (35)	83 (43)	0.25
Calcinosis, n (%)	112 (34)	23 (50)	52 (27)	<0.01
ILD, n (%)	183 (55)	20 (43)	104 (53)	0.26
Ischemic heart disease, n (%)	54 (16)	13 (28)	24 (12)	0.01
Heart failure, n (%)	25 (8)	4 (9)	7 (4)	0.23
PH, n (%)	84 (25)	24 (52)	30 (15)	<0.01
Hypertension, n (%)	38 (11)	9 (20)	15 (8)	0.02
Atrial fibrillation, n (%)	35 (11)	9 (20)	11 (6)	0.005
BMI, kg/m ²	24 (4)	24 (4)	24 (4)	0.16
History of smoking, n (%)	186 (56)	28 (61)	108 (55)	0.62
NT-proBNP at baseline, pmol/l	16 (8-62)	80 (45-247)	11 (6-23)	<0.01
Creatinine at baseline, μmol/l	66 (47-80)	78 (61-97)	64 (55-74)	<0.01

Mortality, n (%)	98 (29)	26 (57)	25 (13)	<0.01
Calcium channel blockers, n (%)	260 (78)	33 (72)	156 (80)	0.22
ACE inhibitors/ARBs, n (%)	124 (37)	24 (52)	56 (29)	<0.01
Anticoagulants, n (%)	89 (27)	24 (52)	24 (12)	<0.01
Beta blockers, n (%)	105 (32)	26 (57)	44 (23)	<0.01
Statins, n (%)	121 (36)	25 (54)	60 (31)	<0.01
Diuretics, n (%)	141 (42)	34 (74)	53 (27)	<0.01
Acetylsalicylic acid, n (%)	124 (37)	23 (50)	61 (31)	0.02

Values are mean (SD) or median (inter quartile range), unless otherwise specified. ACA, anti-centromere antibodies; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; ATA, anti-topoisomerase-I antibodies; BMI, body mass index; ILD, interstitial lung disease; lcSSc, limited cutaneous systemic sclerosis; mRSS, modified Rodnan skin score; PH, pulmonary hypertension.

Table 2: Baseline echocardiographic parameters of SSc patients, stratified by diastolic function, and controls.

	SSc patients		Controls (n=65)
	Diastolic dysfunction (n=46)	Normal diastolic function (n=195)	
LVEF, %	57 (10) [†]	58 (7) [‡]	62 (4)
Mid-range LVEF (40-49 %), n (%)	4 (14) [†]	12 (7)	0 (0)
Low LVEF (<40 %), n (%)	2 (7)	3 (2)	0 (0)
GLS, %	-18.3 (2.8) [†]	-18.4 (2.9) [‡]	-20.3 (2.1)
E, m/s	0.81 (0.32) ^{*,†}	0.72 (0.17)	0.67 (0.17)
A, m/s	0.83 (0.28) ^{*,†}	0.66 (0.20)	0.61 (0.19)
E/A ratio	1.0 (0.5)	1.2 (0.5)	1.2 (0.4)
Deceleration time, ms	199 (58)	194 (40)	193 (38)
e', cm/s	5.0 (1.8) ^{*,†}	8.3 (2.4)	7.7 (2.5)
E/e'	16.9 (5.7) ^{*,†}	9.1 (2.6)	9.4 (3.8)
LAA4C, cm ²	21 (5) ^{*,†}	17 (4)	18 (3)
TAPSE, mm	20 (6) ^{*,†}	24 (5)	25 (4)
FAC, %	33 (11) ^{*,†}	41 (8)	41 (5)
RV basal diameter, mm	4.3 (0.9) ^{*,†}	3.8 (0.6)	3.7 (0.5)
RV free wall strain, %	20 (7) [*]	25 (5)	-
Pathological TRV, (%)	36 (78) ^{*,†}	11 (6)	1 (2)

Mean values are compared by one-way ANOVA with Tukey's post hoc test. Values are mean (SD), unless otherwise specified. * p<0.05 between diastolic dysfunction and normal diastolic function. † p<0.05 between diastolic dysfunction and controls. ‡ p<0.05 between normal diastolic function and controls. A, late transmitral filling velocity; E, early transmitral filling velocity; e', early displacement velocity of the mitral valve; FAC, fractional area change of the right ventricle; GLS, Global longitudinal strain; LAA4C, left atrial area, apical

four-chamber view; LVEF, left ventricular ejection fraction; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity.

Table 3: Prediction of mortality by multivariable cox regression.

	Multivariable cox regression on mortality		
	HR	95 % CI	p-value
DD	3.71	1.69 – 8.14	0.001
DLCO, %	0.96	0.94 – 0.98	0.001
Age	1.05	1.02 – 1.09	0.003
Male sex	1.23	0.54 – 2.80	0.624
mRSS	1.06	1.03 – 1.09	<0.001
TAPSE	0.35	0.17 – 0.73	0.005
NT-proBNP	1.01	1.01-1.01	0.014
C-index	0.89		

DD, diastolic dysfunction; DLCO, diffusion capacity of the lung for carbon monoxide; mRSS, modified Rodnan skin score; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion.

Table 4: Diastolic parameters in patients with available measurements at both baseline and follow-up echocardiography.

	Baseline echocardiography	Follow-up echocardiography	p-value
e', cm/s (n=129)	7.6 (2.8)	7.0 (2.5)	<0.001
E/e' (n=125)	10.4 (4.1)	11.6 (5.9)	0.001
LAVI (n=93)	33.9 (10.5)	36.2 (15.8)	0.119
TRV (n=124)	2.9 (0.8)	3.2 (0.8)	<0.001

Values are mean (SD). DD, diastolic dysfunction; e', early displacement velocity of the mitral valve; LAVI, left atrial volume index; TRV, tricuspid regurgitation velocity.