Advanced echocardiographic imaging in valvular and systemic diseases

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CHAPTER 7

Clinical and echocardiographic associates of all-cause mortality and cardiovascular outcomes in patients with systemic sclerosis

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ABSTRACT

Background: Cardiac involvement is a main cause of mortality in systemic sclerosis (SSc). However, its detection remains challenging using conventional echocardiography. The aim of this study was to identify clinical and echocardiographic parameters, including left ventricular global longitudinal strain (GLS), associated with cardiovascular outcome in SSc patients.

Methods & Results: A total of 408 patients (344 females, 54±14 years) were included. The endpoint included all-cause mortality and hospitalisations for heart failure, myocardial infarction, coronary interventions, device implantations, arrhythmias, cerebral infarction and peripheral ischemic disease. After a follow-up of 39 months [22–66]), the endpoint occurred in 84 patients who were older (59±14 vs 53±14 years, p<0.001), more often male (24% vs 13%, p=0.018), and showed more coronary artery disease (11% vs 3%, p=0.001), Holter-abnormalities (45% vs 24%, p<0.001), worse NT-proBNP (181ng/L [64–654], vs 85ng/L [53–158], p<0.001), diffusing capacity of carbon monoxide ([DLCO] 55%±17 vs 70%±19, p<0.001) and also worse GLS, E/E-ratio, pulmonary pressure and TAPSE (-18.8% [-20.3–-17.6], vs -21.1% [-22.1–-20.0], p<0.001; 9.87 [7.96–12.35], vs 7.88 [6.44–9.68], p<0.001; 31mmHg±12 vs 25mmHg±7, p<0.001; 21mm±4 vs 23mm±4, p=0.017, respectively). In the multivariate Cox regression analyses, GLS was independently associated with the endpoint (HR:1.281, 95%CI:1.172–1.399, p<0.001) together with age, DLCO and NT-proBNP. Comparing patients according to median GLS (≤-20.9% [normal] vs. >-20.9% [impaired]) and the upper value of normal NT-proBNP (≤200 ng/L vs. >200ng/L), endpoint-free survival was worse in patients with impaired GLS *and* elevated NT-proBNP.

Conclusion: In SSc patients, age, DLCO, NT-proBNP and GLS are independently associated with all-cause mortality and cardiovascular hospitalisations and may be useful for risk-stratification and management of these patients.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease which is characterized by microangiopathy and extensive fibrosis, both affecting multiple organs. SSc is associated with increased mortality(1) which is most often due to cardiovascular or pulmonary causes(2-4). According to autopsy reports, primary myocardial involvement is common in SSc and may occur in up to 70% of patients(5). The presence of myocardial fibrosis can lead to significant left ventricular (LV) diastolic and systolic dysfunction, conduction abnormalities and arrhythmias(6-8). However, diagnosis of cardiac involvement in these patients remains challenging, especially at an early stage, as conventional echocardiographic techniques lack sensitivity to detect subtle myocardial dysfunction(9;10). Therefore, in SSc patients, risk stratification tools specifically for cardiovascular outcomes are limited and mainly include LV ejection fraction (LVEF) measurements, pulmonary pressure estimations and heart failure symptoms(9).

Previous studies have demonstrated that 2D speckle tracking strain echocardiography is a reliable and sensitive tool for detecting subtle LV dysfunction in various cardiovascular diseases(10). In particular, global longitudinal strain (GLS) has been introduced in the most recent recommendations for chamber quantification of the American Society of Echocardiography and European Association of Cardiovascular Imaging for the assessment of LV systolic function (11). In SSc patients, measure of GLS showed to be able to identify subtle myocardial dysfunction which was associated with lower functional capacity and presence of arrhythmias(10). However, the prognostic value of GLS in these patients has not yet been explored.

The aim of this study was therefore to identify clinical and echocardiographic parameters, including GLS, associated with all-cause mortality and cardiovascular hospitalisations in a relatively large cohort of SSc patients and in a multi-centre setting.

METHODS

Patient population and protocol

Consecutive SSc patients referred for a specifically designed multidisciplinary health care program at the Department of Rheumatology of the Leiden University Medical Centre (The Netherlands) and of the University Hospital of Zurich (Switzerland) were

evaluated(12;13). Patients were diagnosed according to the classification criteria described by LeRoy et al(14). A baseline echocardiography, defined as the oldest one available, was selected and corresponded with the first out-patient clinic visit at the above-mentioned departments. Only patients with a minimum of one year of follow-up were included in this analysis. Furthermore, patients with a history of myocardial infarction or with severe valvular heart disease were excluded. Written informed consent was obtained at the time of inclusion in the multidisciplinary health care program and additional informed consent was acquired when patients were contacted by telephone to evaluate the occurrence of the pre-specified endpoints.

Baseline clinical variables

Disease related characteristics at baseline included SSc subtype according to leRoy et al(14), modified Rodnan Skin Score, presence of digital ulcers, arthritis, proximal muscle weakness, myositis, calcinosis, pitting scars and pigment changes. General medical history and cardiovascular risk factors were noted. Also, use of heart failure medication and immunosuppressants at baseline were recorded. Laboratory testing was performed systematically and included creatine phosphokinase (CK), erythrocyte sedimentation rate (ESR), renal function (eGFR) and N-terminal pro-brain Natriuretic Peptide (NT-proBNP). Spirometry was performed in all patients according to the American Thoracic Society and the European Respiratory Society guidelines(15;16), and included the percentage of predicted values for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and single breath diffusing capacity of carbon monoxide (DLCO-SB). The presence of lung fibrosis was also assessed with a thoracic high resolution computed tomography and defined with the presence of abnormal findings such as honeycombing, ground-glass opacities or intra-lobular fibrosis(17;18). Furthermore, to assess percentage of predicted peak oxygen consumption (VO_2max), cardiopulmonary exercise testing was performed on an electrically ramped cycle ergometer according to the American Thoracic Society and American College of Chest Physicians guidelines(19). Finally, a 24-hour Holter electrocardiogram (ECG) was performed. Presence of a bundle branch block, ventricular arrhythmias including premature ventricular contraction >100 per day and sustained ventricular tachycardias, and of supraventricular arrhythmias including atrial fibrillation, atrial flutter and premature atrial contraction when more than 7% were recorded (20;21).

Conventional transthoracic echocardiography

Transthoracic echocardiography was performed in all patients in the left lateral decubitus position, using a commercially available system (Vivid 7 and E9; General Electric-Vingmed, Horten, Norway) and a 3.5-MHz or 5MS transducer. Standard M-mode and 2D, colour, pulsed wave and continuous wave Doppler images were acquired and digitally stored in cine-loop format. Off-line analysis was performed using EchoPAC (version 112.0.1; GE Medical Systems, Horten, Norway). LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LV dimensions were measured according to current guidelines(11). Left atrial volume index (LAVI) was measured before the mitral valve opening on the apical four- and two-chamber views according to the biplane Simpson's method and indexed to the patient's body surface area. LV diastolic function was assessed according to current recommendations and included peak early (E) and late (A) diastolic velocities and E-wave deceleration time measured on pulsed wave Doppler recordings of the trans-mitral flow(22). Additionally, E-prime measured with tissue Doppler imaging at the lateral and septal sides of the mitral annulus in the apical four-chamber view was measured an averaged; the E-wave/E-prime ratio was then calculated(22).

Systolic pulmonary arterial pressure (sPAP) was estimated by determining the right ventricular systolic pressure which was calculated by adding the peak tricuspid regurgitation gradient to the right atrial pressure which was estimated by the inferior vena cava diameter and degree of respiratory collapse(23). Right ventricular function was evaluated by measuring the tricuspid annular plane systolic excursion (TAPSE)(24). Presence of pericardial effusion was also recorded.

Two-dimensional speckle tracking strain echocardiography

LV GLS was measured as previously described by using the four-, two- and three chamber views in order to obtain measurements of all segments of the LV (11;25). The LV GLS was automatically calculated as the average peak systolic strain of 17 LV segments (Figure 1.) Negative values are used to express LV GLS as it represents shortening of the myocardial wall: a more negative value represents better myocardial deformation.

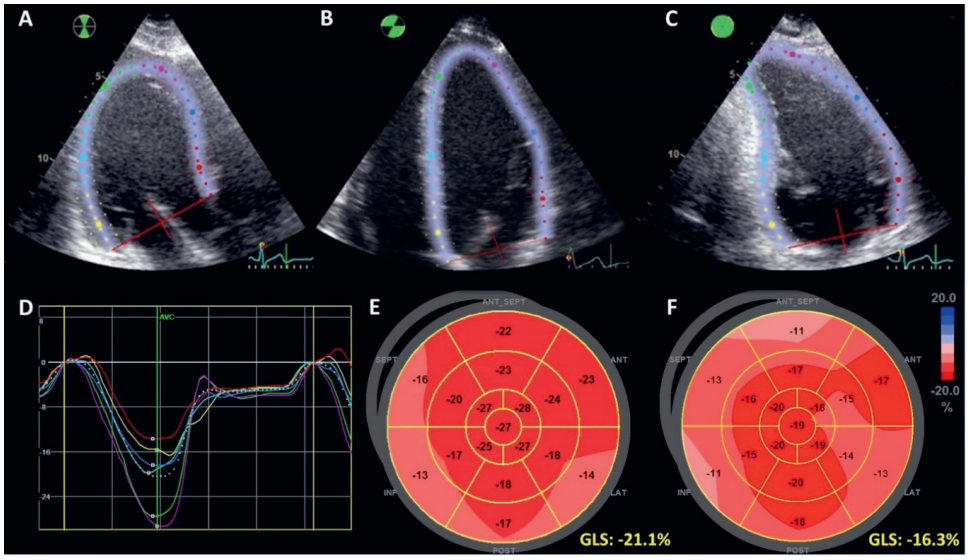

Figure 1. *Global longitudinal strain of the left ventricle measured by 2D speckle tracking strain analysis applied to a three-chamber apical view (A), four-chamber apical view (B) and a two-chamber apical view (C). D: example of curves of longitudinal strain per segment and averaged among the segments (dotted line). E: A bulls' eye display of segmental peak systolic longitudinal strain values, colour coded (dark red as preserved GLS, to pink as impaired GLS) in a patient with a normal GLS and no endpoint. Global longitudinal strain (GLS) is calculated by averaging the 17 segments. F: Example of a patient with impaired GLS in whom an endpoint occurred 21 months later.*

Follow-up and endpoint

The endpoint of this study was defined as either all-cause mortality or hospitalisations for cardiovascular reasons which included pacemaker/cardioverter defibrillator implantations, development of heart failure, myocardial infarction, arrhythmias, angina pectoris, percutaneous coronary interventions, cerebral infarctions and peripheral ischemic disease. Endpoint data was obtained by reviewing the electronic information system and by retrieval of survival status through the municipal civil registries. If the last available follow-up data were dated more than one year ago or incomplete, patients and their general practitioners were contacted by telephone for more recent information.

Statistical analysis

Data analysis was performed using SPSS® software version 23.0 (IBM, Armonk, NY, USA). Continuous variables are presented as mean ± SD or as median with interquartile

ranges (IQR) according to the presence of normal distribution. Categorical data are presented as frequencies and percentages. Continuous variables were compared using one-way analysis of variance (ANOVA), applying the Bonferroni's post-hoc analysis, or the Kruskal-Wallis one-way analysis of variance. Categorical variables were compared with the Chi-square test. Variables associated with endpoints, defined as combined all-cause mortality and cardiovascular hospitalisations, were identified using the Cox proportional hazards model; a baseline model included extra-cardiac variables clinically relevant and significant in the univariate analyses. Limited by the number of events, variables that were significant in the baseline "clinical" model were used for the additional multivariate models. Echocardiographic parameters which were significant in the univariate analyses were added in groups based on the parameter type. Patients were divided according to the median of LV GLS and elevated NT-proBNP according to local reference values (>200ng/L) and the cumulative event rates for all-cause mortality or cardiovascular hospitalisation were estimated with the Kaplan-Meier curves and compared with log-rank tests. P-values <0.05 were considered significant.

RESULTS

Clinical characteristics and endpoint

A total of 408 SSc patients were included and their baseline clinical characteristics are shown in Table 1. At total of 374 patients (92%) fulfilled the ACR 2013 criteria(26). After a median follow-up duration of 39 months (IQR: 22 – 66), 37 patients died, 57 patients were hospitalised for cardiovascular reasons and the combined endpoint of all-cause mortality and cardiovascular hospitalisations occurred in 84 (22%) patients. As shown in Table 1, patients who experienced the endpoint were slightly older and more often male. No significant differences were observed in time since onset of Raynaud and non-Raynaud symptoms or SSc type between patients with and without an event. Patients in whom an event occurred also had a worse baseline clinical profile in terms of disease activity (e.g. pitting scars), presence of previous coronary artery disease (excluding myocardial infarction), Holter ECG abnormalities, laboratory testing (ESR and NT-proBNP) abnormalities, pulmonary and functional testing and use of heart failure and immunosuppressive medication (Table 1).

Table 1. Patient clinical characteristics.

Characteristics	Total (N=408)	Patient groups according to combined endpoint		P-value
		Endpoint (N=84)	Endpoint free (n=324)	
Age Yr, mean ± SD	54 ± 14	59 ± 14	53 ± 14	<0.001
Female, n (%)	344 (85)	64 (76)	280 (87)	0.018
Body Surface Area m^2, mean ± SD	1.78 ± 0.19	1.76 ± 0.18	1.79 ± 0.20	0.174
Time since Raynaud Yr median (IQR)	8.7 (3.1–17.9)	10.0 (2.9 – 19.9)	8.7 (3.2 – 16.7)	0.564
Time since non-Raynaud Yr median (IQR)	4.0 (1.3–10.3)	3..0 (1.0 – 12.0)	4.0 (1.0 – 9.5)	0.920
Diffuse cutaneous SSc, n (%)	121 (29)	28 (33)	92 (28)	0.385
Disease activity, n (%)				
mRSS>15	40 (10)	10 (12)	30 (9)	0.851
Digital ulcers	103 (25)	25 (30)	78 (24)	0.271
Arthritis	45 (11)	12 (14)	33 (10)	0.285
Proximal muscle weakness	38 (9)	9 (11)	29 (9)	0.619
Myositis	8 (2)	1 (1)	7 (2)	0.460
Calcinosis	60 (15)	16 (19)	44 (14)	0.459
Pitting scars	159 (39)	43 (51)	116 (36)	0.006
Lung fibrosis	137 (34)	33 (39)	104 (32)	0.221
Medical history & Cardiovascular risk factors, n (%)				
Hypertension	114 (28)	28 (33)	86 (27)	0.235
Diabetes	17 (4)	5 (6)	12 (4)	0.361
(History of) smoking	172 (42)	36 (43)	136 (42)	0.959
Coronary artery disease	17 (4)	9 (11)	8 (3)	0.001
Prior/current pericarditis	17 (4)	6 (7)	11(3)	0.127
Holter abnormalities	114 (28)	38 (45)	76 (24)	<0.001
History of renal crisis	14 (3)	4 (5)	10 (3)	0.459
Laboratory tests				
Creatine Phosphokinase U/L, median (IQR)	86 (61–124)	84 (64 – 118)	86 (61 – 125)	0.722
ESR mm/hour, median (IQR)	14 (6–29)	24 (14 – 46)	11 (6 – 25)	<0.001
eGFR ml/min/1.73m2, mean ± SD	89 ± 28	84 ± 31	90 ± 26	0.068
NT-proBNP ng/L, median (IQR)	96 (54 – 184)	181 (64 – 654)	85 (53 – 158)	<0.001
Cardiopulmonary function tests, mean ± SD				
FVC *% of predicted*	101 ± 22	92 ± 19	104 ± 21	<0.001
FEV1 *% of predicted*	96 ± 19	88 ± 17	97 ± 19	0.002
DLCO-SB *% of predicted*	67 ± 20	55 ± 17	70 ± 19	<0.001
VO2max % of predicted*	87 ± 24	79 ± 22	89 ± 24	0.003
Mean heart rate, beats per minute	79 ± 10	78 ± 10	79 ± 8	0.522
Cardiovascular medication, n (%)				
ACEi/ARB	152 (37)	48 (57)	104 (32)	<0.001
Beta-blocker	32 (8)	18 (21)	14 (4)	<0.001
Ca^{2+} channel blocker	176 (43)	41 (49)	135 (42)	0.318
Diuretics	51 (13)	16 (19)	35 (11)	0.053
Immunosuppressive medication, n (%)				
Corticosteroids	55 (14)	18 (21)	37 (12)	0.017
Cyclophosphamide	5 (1)	1 (1)	4 (1)	0.956
Methotrexate	52 (13)	10 (12)	42 (13)	0.828
Azathioprine	15 (4)	7 (8)	8 (3)	0.013

ACEi = Angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; DLCO-SB = diffusing capacity for carbon monoxide single breath; eGFR = estimated Glomerular Filtration Rate; ESR = Erythrocyte Sedimentation Rate; FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; mRSS = Modified Rodnan skin thickness score; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; VO2max = Maximal oxygen uptake. * only available in patients of the Leiden University Medical Centre

Echocardiographic characteristics and endpoint

All baseline echocardiographic parameters are summarized in Table 2. Patients who experienced the endpoint had a slightly lower LVEF compared to those who remained endpoint-free; however, LVEF still remained within normal ranges. Furthermore, interventricular septum and posterior wall thickness of the LV were thicker and LAVI was larger in patients with the endpoint. Also in these patients, right ventricular function (as assessed by TAPSE) and LV diastolic function, as reflected by higher E/E-prime ratio, and sPAP were significantly worse as compared to patients without the endpoint. As measured by 2D-speckle tracking strain echocardiography, LV GLS was also significantly worse in patients who experienced the endpoint (-18.8%, IQR: -20.3 – -17.6, versus -21.1%, IQR: -22.1 – -20.0, $p<0.001$).

Independent associates of the endpoint

According to univariate Cox proportional hazard analyses, among the clinical characteristics age, female, pitting scars, coronary artery disease, Holter ECG abnormalities, ESR, eGFR, NT-proBNP, FVC, FEV1, DLCO-SB and VO_2max were significantly associated with the endpoint (Table 3). Echocardiographic parameters significantly associated with the endpoint in the univariate analyses were LVESV, LAVI, E/E-prime ratio, sPAP, TAPSE and LV GLS (Table 3). Clinical characteristics significantly associated with the endpoint at the univariate analysis were included in a multivariate model where age, female, NT-proBNP and DLCO-SB remained independently associated with the endpoint, while coronary artery disease and Holter ECG abnormalities did not (Table 4). The above-mentioned multivariate model formed the basic clinical model for further multivariate analyses. When LAVI, E/E-prime and sPAP, reflecting LV diastolic function and pulmonary pressures, were added to the basic clinical model, none was longer independently associated with the endpoint. Also, the chi-square values did not increase significantly when these parameters were added to the basic clinical model (figure 2). However, when TAPSE and LV GLS, reflecting systolic function of the right and left ventricle were added to the model, LV GLS remained independently associated with the endpoint together with age, female, NT-proBNP and DLCO-SB, and the chi-square increased significantly from the previous model indicating that these variables have incremental value over clinical and conventional parameters for risk stratification in SSc patients (Figure 2).

Table 2. Baseline echocardiographic parameters

		Patient groups according to combined endpoint		
	Total (n=408)	**Endpoint (n=84)**	**Endpoint free (n=324)**	**P-value**
Conventional parameters				
LVEF %, mean ± SD	62 ± 7	60 ± 7	62 ± 6	0.015
LVEDV ml, median (IQR)	83 (67–99)	86 (67 – 99)	82 (67 – 99)	0.431
LVESV m, median (IQR)	30 (24–39)	33 (25 – 42)	30 (24 – 38)	0.107
IVST mm, mean ± SD	9 ± 2	8 ± 2	9 ± 2	0.001
LVEDd mm, mean ± SD	47 ± 6	47 ± 6	47 ± 5	0.711
PWT mm, mean ± SD	9 ± 2	9 ± 2	8 ± 2	0.004
LAVI ml, median (IQR)	35 (28–46)	39 (30 – 52)	34 (27 – 43)	0.009
E/A ratio, median (IQR)	1.07 (0.84 – 1.32)	1.03 ± 0.78	1.08 (0.88 – 1.33)	0.090
E-prime cm/sec, mean ± SD	10.19 ± 3.39	9.50 ± 3.40	10.28 ± 3.39	0.406
E/E-prime ratio, median (IQR)	8.28 (6.65 – 10.23)	9.87 (7.96 – 12.35)	7.88 (6.44 – 9.68)	<0.001
sPAP mmHg, mean ± SD	26 ± 8	31 ± 12	25 ± 7	<0.001
sPAP>35 mmHg, n (%)	48 (12)	24 (29)	24 (7)	<0.001
TAPSE mm, mean ± SD	23 ± 4	21 ± 4	23 ± 4	0.017
Pericardial Effusion, n (%)	17 (5)	6 (7)	16 (5)	0.434
2D Speckle tracking strain analyses				
LV GLS %, median (IQR)	-20.9 (-22.0 - -19.5)	-18.8 (-20.3 – -17.6)	-21.1 (-22.1 – -20.0)	<0.001

GLS = Global Longitudinal Strain; IVRT = Isovolemic relaxation time; IVST = Interventricular Septum Thickness; LAVI, Left Atrial Volume index. LV = Left Ventricle; PWT = Posterior Wall Thickness; sPAP = systolic Pulmonary Artery Pressure; TAPSE = Tricuspid annular plane systolic excursion

Table 3. Univariate Cox proportional hazards analyses for the combined endpoint of all-cause mortality and cardiovascular hospitalisations.

N=408	Univariate analysis		
Variables	**HR**	**95% CI**	**P value**
Patient characteristics			
Age	1.041	1.023-1.059	<0.001
Female	0.591	0.357-0.978	0.041
Years since Raynaud	1.010	0.994-1.026	0.229
Time since non-Raynaud	1.022	0.999-1.045	0.065
Disease activity			
MRSS>15	1.345	0.691-2.615	0.383
Digital ulcers	1.426	0.890-2.284	0.140
Arthritis	1.659	0.898-3.067	0.106
Proximal muscle weakness	1.659	0.828-3.325	0.154
Myositis	0.456	0.063-3.278	0.435
Calcinosis	1.210	0.698-2.097	0.497
Pitting scars	1.815	1.173-2.808	0.007
Lung fibrosis	1.160	0.747-1.803	0.508
Medical history & Cardiovascular risk factors			
Hypertension	1.565	0.993-2.466	0.054
Diabetes	1.030	0.415-2.558	0.949
(History of) smoking	0.904	0.584-1.400	0.904
Coronary artery disease	3.065	1.530-6.140	0.002
Pericarditis	1.858	0.809-4.270	0.144
Holter ECG abnormalities	1.971	1.259-3.086	0.003
Renal crisis	1.217	0.445-3.328	0.702
Laboratory tests			
Creatine phosphokinase	1.000	0.999-1.002	0.641
ESR	1.016	1.009 - 1.023	<0.001
eGFR	0.992	0.984 – 1.000	0.048
NT-proBNP per 100ng/L	1.121	1.091 – 1.151	<0.001
Cardiopulmonary function tests			
FVC *% of predicted*	0.984	0.973-0.994	0.003
FEV1 *% of predicted*	0.986	0.973-0.998	0.023
DLCO-SB *% of predicted*	0.973	0.962-0.984	<0.001
VO2max % of predicted*	0.984	0.974-0.994	0.003
Mean heart rate	0.999	0.974-1.024	0.908
Echocardiographic parameters			
LV ejection fraction	0.970	0.941-1.001	0.057
LVEDV	1.006	0.998-1.014	0.161
LVESV	1.017	1.003-1.031	0.015
LAVI	1.024	1.003-1.045	0.025
E/A ratio	0.655	0.345-1.247	0.198
E-prime	0.967	0.821-1.140	0.691
E/E-prime ratio	1.081	1.028-1.137	0.002
sPAP	1.056	1.038-1.074	<0.001
TAPSE	0.936	0.883-0.993	0.027
Pericardial Effusion	1.302	0.567-2.992	0.534
LV GLS	1.372	1.282-1.468	<0.001

For abbreviations see table 1 or 2.

Table 4. Multivariate Cox proportional hazards analyses for the combined endpoint of all-cause mortality and cardiovascular hospitalisations.

N=408	**Multivariate analyses**								
	Baseline model			Clinical model + diastolic parameters + sPAP			Clinical model + systolic parameters		
Variables	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	1.035	1.012 – 1.058	0.003	0.997	0.942 – 1.055	0.911	1.029	1.006 – 1.052	0.014
Female	0.439	0.248 – 0.777	0.005	0.228	0.052 – 0.228	0.052	0.527	0.302 – 0.922	0.025
Coronary artery disease	1.282	0.487 – 3.376	0.615						
Holter ECG abnormalities	1.550	0.929 – 2.589	0.094						
NT-proBNP per 100ng/L	1.048	1.027 – 1.070	<0.001	1.073	1.007 – 1.143	0.030	1.048	1.028 – 1.069	<0.001
DLCO-SB *% of predicted*	0.976	0.964 – 0.988	<0.001	0.995	0.958 – 1.034	0.793	0.973	0.961 – 0.986	<0.001
LAVI				1.066	0.996 – 1.140	0.063			
E/E-prime ratio				0.860	0.660 – 1.121	0.264			
sPAP				0.969	0.913 – 1.092	0.969			
TAPSE							1.043	0.976 – 1.114	0.218
LV GLS							1.281	1.172 – 1.399	<0.001

For abbreviations see table 1 or 2.

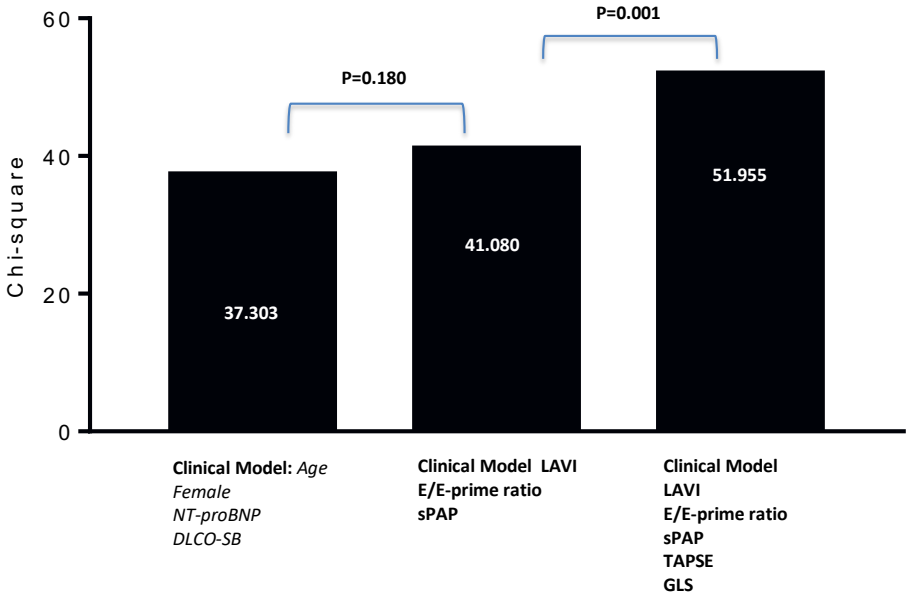

***Figure 2**. Multivariate Cox proportional hazards analyses and Chi-square values presented per model for combined all-cause mortality and cardiovascular hospitalisations*

Taking into consideration the cardiac-specific parameters independently associated with the endpoints (LV GLS and NT-pro BNP), patients were dichotomised according to the median values of LV GLS (≤-20.9% [normal] vs. >-20.9% [more impaired]) and the upper value of normal NT-proBNP (≤200 ng/L vs. >200ng/L). Kaplan-Meier curves (Figure 3) showed worse survival-free from the endpoints in patients with impaired LV GLS values and in the 87 patients with elevated NT-proBNP. When both parameters were considered, elevated NT-proBNP further affected prognosis when LV GLS was impaired. In contrast, when LV GLS was not impaired, prognosis remained good even in the presence of elevated NT-proBNP levels (Figure 3).

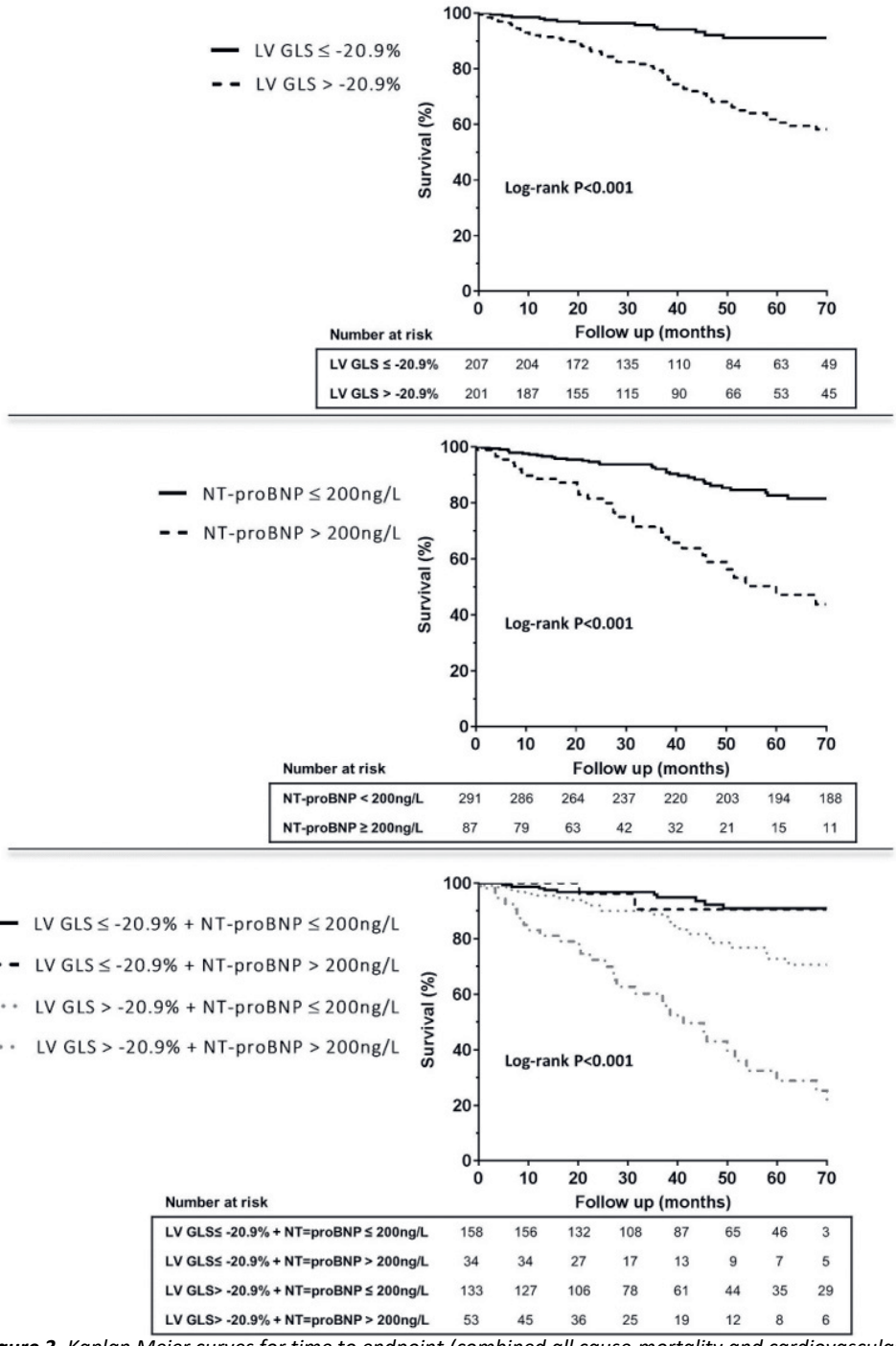

Figure 3. *Kaplan Meier curves for time to endpoint (combined all cause-mortality and cardiovascular hospitalisations) according to the median of left ventricular global longitudinal strain (LV GLS), to elevated NT-proBNP (>200ng/L) and combination of both parameters.*

DISCUSSION

The present study assessed the association of clinical and echocardiographic parameters with all-cause mortality and cardiovascular hospitalisations as endpoints in a relatively large group of SSc patients from two different university centres. LV function, as measured by LV GLS, together with age, gender, DLCO-SB and NT-proBNP, was independently associated with the combined endpoint.

Risk stratification in systemic sclerosis patients

To date, several multi-centre studies have shown that cardiac involvement is one of the most important causes of morbidity and mortality in SSc patients(2-4). Furthermore, the risk of developing cardiovascular disease has been shown to be significantly higher in SSc patients as compared to the general population(27). The incidence of cardiovascular disease is also increasing in this population since SSc patients are less likely to die of SSc-specific complications as a result of improvements in treatment for renal crisis and pulmonary hypertension(27). However, clinical presentation and prognosis of SSc are highly heterogeneous which makes identification of patients at high risk for cardiovascular events crucial in order to optimize patient management. Large studies on risk stratification in SSc patients mainly focussed on clinical characteristics and only on few cardiac-specific parameters to estimate prognosis(1;3;4). A probable explanation is that despite its importance, cardiac involvement remains difficult to detect and in current clinical practice the diagnosis is based only on clinical symptoms and conventional echocardiography(1;3;4). From the recently published data of the EUSTAR database for example(4), in which a mortality of 9.6% was reported mainly due to cardiopulmonary disease, only dyspnoea symptoms and LVEF <50% were included in the multivariate survival analysis. This analysis demonstrated an independent prognostic value of dyspnoea and LVEF<50% together with age, gender, diffuse cutaneous SSc, elevated C reactive protein, interstitial lung disease, DLCO-SB, FVC, proteinuria, scleroderma renal crisis, digital ulcers and joint involvement(4). Of note, known cardiovascular risk factors, such as systemic hypertension, pulmonary hypertension and LV diastolic function were not significantly associated with mortality. However, an impaired LVEF and development of heart failure symptoms represent an advanced stage of cardiac involvement, whereas, risk stratification should ideally help

identify patients at higher risk in which earlier treatment can still change the natural course and prognosis of the disease. Therefore, novel cardiac-specific prognostic markers are needed to improve risk stratification in these patients. Nevertheless, evaluations of the prognostic value of other echocardiographic parameters are scarce in literature. Only small studies specifically assessed the value of LV diastolic dysfunction, which was shown to be more common than LV systolic dysfunction and was associated with increased mortality(28-32). In the current study, LV diastolic function parameters and sPAP were associated with the combined endpoint but only in acunivariate analysis. In contrast, LV systolic dysfunction in SSc patients has been shown to be less common when measured by conventional LVEF, most likely due to its low sensitivity for detecting subtle myocardial systolic dysfunction(9;28;33;34). In the current study, LVEF values were within normal ranges both in patients with and without the endpoint and LVEF was not significantly associated with mortality or cardiovascular hospitalisations.

Novel cardiac-specific parameters associated with prognosis: LV GLS and NT-proBNP

A previous study in SSc patients demonstrated that LV GLS, measured by 2D speckle tracking strain echocardiography, is a more sensitive method for detecting LV systolic dysfunction, which is more prevalent than previously described(10). In these patients, impaired LV GLS reflects subtle LV dysfunction (most often with preserved LVEF) which is secondary to different pathophysiological processes(6-9;35;36): e.g. diffuse or patchy myocardial fibrosis related to the microangiopathy; myocardial stunning due to repeated focal ischemia caused by abnormal vasoreactivity, and finally, the occurrence of a peri-myocarditis. Therefore, LV GLS represents a promising novel tool to improve detection of LV systolic dysfunction in these patients and the current study is the first to further demonstrate the association of LV GLS with all-cause mortality and cardiovascular hospitalisations in a population with a similar mortality rate (9%) and a comparable follow-up of the EUSTAR database(4).

In SSc patients, NT-proBNP has also been demonstrated as an important biomarker associated with pulmonary arterial hypertension, renal crisis and cardiac involvement(37-40). Also, its prognostic value for all-cause mortality has been reported in these patients(41). The current study confirmed the independent association of NT-proBNP with

all-cause mortality and cardiovascular hospitalisations, which was stronger than for conventional echocardiographic measurements such as LVEF and sPAP. Furthermore, the present study demonstrates the utility of combining this biomarker with LV GLS for further risk assessment in these patients. When LV GLS was impaired, elevated NT-proBNP further increased the risk for the combined endpoint. However, when LV GLS was not impaired, NT-proBNP had no further impact on prognosis. This observation may have several explanations. First, in case of cardiac involvement changes in LV GLS may occur prior to changes in NT-proBNP and may therefore be more sensitive. The elevation of NT-proBNP suggests a more advanced stage of cardiac involvement possibly with elevated pulmonary pressure and/or significant LV diastolic dysfunction and/or arrhythmias. Second, if LV GLS was not impaired, (mildly) elevated NT-proBNP had no significant impact on prognosis maybe because more likely due to e.g. impaired renal function, volume overload or only mild LV diastolic dysfunction.

Clinical implications

In SSc, early diagnosis of cardiac involvement by LV GLS may provide the opportunity to select which patients need further diagnostic assessment (e.g. cardiac magnetic resonance imaging, right heart catheterisation, 24 hours Holter ECG monitoring), closer follow-up, and eventually specific treatment in order to delay or halt the process of developing myocardial fibrosis and overt cardiac dysfunction. Additionally, the current study demonstrated that LV GLS is not only a useful tool for detecting subtle LV myocardial involvement in SSc, but also for identifying patients at higher risk for mortality and cardiovascular events and may therefore optimize risk stratification. In particular, an integrative approach using LV GLS and NT-proBNP may improve detection or even exclusion of (primary) cardiac involvement and optimize patient management. If so, cardiac involvement may be more likely in those patients with elevated NT-proBNP together with impaired LV GLS. Further studies are necessary to investigate the distinguishing capabilities of this approach. Furthermore, in the specific group of patients referred for autologous stem cell transplantation or for chemotherapy, an accurate screening tool to assess LV function and monitor it over time, would be of great clinical value since cardiac involvement has been demonstrated to be an important cause of morbidity and mortality following these treatments(42).

Limitations

The following limitations of the study should be mentioned: 1) specific analyses for myocardial ischemia were not systematically performed; however, all patients underwent cardiopulmonary exercise testing without showing signs of myocardial ischemia making its presence unlikely; 2) treatment strategies were not taken into account during follow-up, and the potential association with changes in cardiac function remains unclear; however, considering the absence of strict recommendations, therapeutic changes were also not included in previously published prognostic models(4); 3) right heart catheterisation was only performed when clinically indicated and therefore in a limited number of patients. However, sPAP has proven to be a robust alternative measure for pulmonary arterial hypertension(43) and was measured in all patients; 4) finally, the small number of patients with a combined endpoint led to a limited amount of variables that could be included in the multivariate analysis. Results of the current study should be therefore confirmed in larger, prospective, multicentre studies with longer follow-up.

CONCLUSIONS

In SSc patients, LV GLS was strongly associated with all-cause mortality and cardiovascular hospitalisations along with age, DLCO-SB and NT-proBNP. In particular, an integrative approach using LV GLS and NT-proBNP showed to improve risk stratification in these patients and may be of additional value to initiate closer surveillance which may result in earlier and more adequate treatment strategies.

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