Does arterial stiffness predict mortality in patients with scleroderma: a long-term follow-up study

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Abstract. – **OBJECTIVE:** Subclinical macrovascular impairment, which has been evaluated with various arterial stiffness (AS) parameters, has been defined in patients with systemic sclerosis (SSc). However, studies investigating the relationship between AS and clinical endpoints in SSc are lacking. This study aims to determine the prognostic value of AS parameters to predict all-cause mortality in SSc patients.

PATIENTS AND METHODS: AS parameters [carotid-radial pulse wave velocity (PWV) and augmentation index (AIx)] were assessed *via* applanation tonometry. The prognostic value of these parameters was quantified in patients with SSc (n=60) without pulmonary arterial hypertension (PAH) and obvious cardiac involvement against survival.

RESULTS: The overall median follow-up time was 10.3 years, and a 29.4% (n=20) mortality was observed. Four significant predictors of mortality were observed: lung involvement (HR 2.608, p=0.04), the lower level of predicted carbon monoxide diffusing capacity (HR 0.978, p=0.03), lower level of estimated glomerular filtration rate (HR 0.979, p=0.04), and elevated serum C reactive protein (CRP) levels (HR 1.066, p<0.001). Among these variables, elevated CRP was found to be an independent predictor of all-cause mortality. AS parameters were not associated with all-cause mortality (HR 1.014, p=0.6 for AIx and HR 0.737, p=0.19 for PWV, respectively).

CONCLUSIONS: Long-term data failed to demonstrate the prognostic value of AS parameters in predicting all-cause mortality in SSc patients. The exact mechanisms of cardiovascular (CV) mortality in SSc patients deemed to be atherosclerotic in origin needs to be determined in large-scale studies.

Key Words:
Arterial stiffness, Augmentation index, Pulse wave velocity, Mortality, Scleroderma.

Introduction

Scleroderma, also known as systemic sclerosis (SSc), is a progressive connective tissue disorder marked by severe fibrosis, microvascular impairment, and immune system dysregulation[1]. It can impact numerous organ systems and exhibit a wide range of variations in clinical symptoms, autoantibody profiles, disease progression, therapeutic response, and survival. It is frequently separated into two subtypes: limited cutaneous and diffuse cutaneous SSc[2]. In the limited cutaneous SSc, fibrosis mostly affects the face and distal limbs, whereas Raynaud's phenomenon often manifests months to years prior to skin and visceral involvement. In contrast, diffuse SSc progresses quickly, resulting in severe skin fibrosis, tendon contractures, and the early onset of problems involving the visceral organs. Pulmonary arterial hypertension (PAH) is an important feature of the disease which occurs equally in both types[3].

Compared to clinical diagnosis, post-mortem findings[4] revealed a greater frequency of cardiac involvement in subjects with SSc. A variety of cardiac abnormalities might be present in these patients, including myocardial fibrosis and inflammation, diastolic and systolic dysfunction, decreased perfusion, and, less commonly, valvular lesions[5]. However, only 10-30% of cases with cardiac involvement are symptomatic, and the majority of cases (approximately 70%) have a silent course[6]. Almost 1/3 of deaths in SSc are related to cardiovascular (CV) causes and cardiac involvement is a sign of aggressive disease.

In recent years, the mortality causes of SSc have changed; those due to disease-related complications (scleroderma-related renal crisis, PAH, and pulmonary fibrosis) have decreased, while death rates due to atherosclerotic cardio- and cerebrovascular disease have gradually increased. Analyzing the surrogate markers of CV disease (CVD) may be helpful in understanding the causes of the increase in CV events in SSc. Parameters of arterial stiffness (AS) has been recognized as a reliable marker of early vascular aging and predicted CV outcomes and all-cause

mortality[7]. It is demonstrated that patients with SSc have more prevalent macrovascular involvement compared to controls evaluated by different non-invasive AS parameters[8]. However, studies investigating the relations between AS and clinical endpoints, including CV events and all-cause mortality, are lacking. This report aimed to define the ability of peripheral AS parameters to predict mortality in SSc patients without PAH and obvious cardiac involvement.

Patients and Methods

Subjects and Data Collection

Sixty consecutive patients diagnosed with SSc in the Dokuz Eylul University Department of Rheumatology and Immunology were enrolled between January 1, 2011, and January 1, 2012. Patients were followed until December 1, 2022. Patients with atherosclerotic CV disease, chronic heart failure, significant valvular heart disease, pericardial effusion, permanent and paroxysmal atrial fibrillation, electrocardiographic (ECG) abnormalities, diastolic dysfunction, and PAH were excluded from this study. Disease classification, skin involvement, and lung involvement were defined according to the updated ACR/EULAR classification criteria[2].

The first self-reported Reynaud phenomenon was used to determine the age of disease onset. Medical history, medication use, smoking status, anthropometric data, and laboratory data, including autoantibodies, were obtained from institutional medical data. Hypertension (HT) is specified as having a systolic blood pressure (BP) of more than 140 mmHg or a diastolic BP of more than 90 mmHg, or the current use of a BP-lowering drug. Diabetes mellitus (DM) is specified as a fasting serum glucose of 126 mg/dL or higher or the present use of antidiabetic medication. Hyperlipidemia (HL) is specified as having fasting low-density lipoprotein cholesterol levels of more than 100 mg/dL or the present use of lipid-lowering medication. All-cause mortality was preferred as the endpoint to avoid misclassification of the cause of death. The duration of follow-up was defined as the interval between the time of echocardiography and AS measurement and the time of death or the final clinical visit.

This study was carried out in compliance with the rights outlined in the Declaration of Helsinki and received approval from the local Medical Ethics Committee. All patients provided their written informed consent.

Echocardiographic Examination

An experienced cardiologist performed all echocardiographic examinations using a Philips HD 11 XE ultrasound system (Philips, Andover, MA, USA) with a 3.2 MHz transducer. Using the parasternal long-axis view, the left atrium diameter (LAd), left ventricular end-systolic diameter (LVESD), and left ventricular end-diastolic diameter (LVEDD) were measured. The biplane summation-of-disks method was used for the estimation of LV volumes and ejection fraction (LVEF) from the apical views. The left atrial (LAA) and right atrial areas (RAA) were measured at the end of the systole from the apical four-chamber (4C) view. The right ventricle (RV)-focused apical 4C view was used for the linear longitudinal end-diastolic dimension of RV (RVd). The RV fractional area change (RVFAC) was calculated from the apical 4C view as (end-diastolic area – end-systolic area)/end-diastolic area x 100%. An M-mode cursor was placed in the apical 4C view down the lateral RV wall to the tricuspid annulus. Tricuspid annular plane systolic excursion (TAPSE) was defined as the largest displacement of the tricuspid annulus during systole.

The mitral flow velocities were measured using the pulsed-wave (PW) Doppler in the apical 4C view. The early diastolic peak E wave (E), atrial contraction wave (A), and deceleration time (EDT) were measured, and the E/A ratio was determined.

The lateral tricuspid annular and the medial and lateral mitral annular velocities were measured using tissue Doppler imaging (TDI) in the apical 4C view. LV systolic (LV S') and diastolic (LV E'), and RV systolic (RV S') velocities were recorded. For diastolic LV filling performance, E/E' was calculated.

The RV and LV Tei indexes were calculated using TDI velocity waveforms as well. The sum of the isovolumetric relaxation duration and contraction duration divided by the ejection duration was used to compute the LV Tei index. A similar method was also used for the determination of the RV Tei index.

Measurement of Arterial Stiffness

SphygmoCor applanation tonometry was used to measure the radial artery pressure waveforms (AtCor Medical, West Ryde, NSW, Australia). The applanation tonometry device automatically measured central aortic pressure, pulse pressure (PP), aortic pressure augmentation, and augmentation index (AIx). AIx was calculated as aortic pressure augmentation divided by PP. By consecutively recording electrocardiography-gated

carotid and radial artery waveforms, aortic pulse wave velocity (AoPWV) was calculated using the same device. The tape measure was used for the measurement of the path length. The path length was determined as (distance from the suprasternal notch to the carotid artery) – (distance from the suprasternal notch to the radial artery). This length was divided by transit time for the calculation of AoPWV. Echocardiographic examination and arterial stiffness measurements were performed consecutively in each participant during the morning fasting period.

Statistical Analysis

The statistical analysis was carried out using SPSS version 26 (IBM Corp., Armonk, NY, USA). Histograms and the Kolmogorov-Smirnov test validated the normal distribution of continuous data. The continuous data were shown as means ± standard deviations, and median (interquartile range). The Student t-test for normally distributed variables, the Mann-Whitney U-test for non-normally distributed variables, and the Chi-square test for categorical data were used to assess differences across groups. Using Receiver-operating characteristic (ROC) curves, the effectiveness of peripheral AS measures in predicting all-cause mortality was evaluated. The values of the area under the curve (AUC) were estimated. Using univariate and multivariate Cox proportional-hazard models, we estimated 95% confidence intervals (CI) for hazard ratios (HR). Variables from univariate analyses with $p<0.1$ were utilized to develop models. A p-value <0.05 was considered statistically significant.

Results

Clinical and Echocardiographic Characteristics

Sixty consecutive SSc patients were enrolled in this study. The overall median follow-up time was 10.3 years, and a 29.4% (n=20) all-cause mortality was observed. The study population consisted of 88.3% women with a mean age of 49.1±12.3 years. Twenty-nine (48.3%) patients had limited scleroderma, while 31 (51.7%) patients had diffuse scleroderma. 27 (45%) patients had lung involvement, and 29 (48.3%) had skin involvement. Table I represents the baseline characteristics of all patients.

Analysis of baseline characteristics between patients alive and deceased patients revealed some differences (Table I). Compared to survivors, deceased patients were older (p=0.003) and had a greater rate of lung involvement (p=0.03). Time from first Reynaud's symptoms was higher in the deceased group. Deceased subjects had lower predicted forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) and carbon monoxide diffusing capacity of the lung (DLCO) levels (p=0.045 and p=0.02, respectively) and had higher baseline serum CRP levels (p=0.04). Traditional CV risk factors, including smoking, HT, DM, and HL, were similar between alive and deceased patients.

Comparison of echocardiographic data at baseline revealed similar results between alive and deceased patients (Table II). LVEF was preserved in all patients. LV dimensions and LV Tei index were normal and comparable between groups. RV diameters, RV Tei index, and systolic pulmonary artery pressure (SPAP) values were normal and similar between the two groups.

Arterial Stiffness Parameters

AS measurements were not significantly different between deceased and alive patients (Table III). Moreover, none of the arterial stiffness parameters revealed prognostic performance in predicting all-cause mortality in ROC curve analysis [AUC=0.476; 95% CI: 0.315-0.636, p=0.76 for AIx and AUC=0.634; 95% CI: 0.477-0.792, p=0.09 for PWV (Figure 1)].

Associations of All-Cause Mortality

The overall survival rates were 98% at 1 year, 93% at 3 years, 88% at 5 years, and 68% at 10 years (Figure 2). The baseline lower level of predicted DLCO and baseline lower level of estimated Glomerular filtration rate (eGFR) were significant predictors of all-cause mortality in univariate Cox regression analysis [HR 0.978 (0.959-0.998), p=0.03, HR 0.979 (0.960-0.999), p=0.04, respectively]. Patients with lung involvement had a 2.61 times greater risk of mortality than those without lung involvement [HR 2.608 (1.0.39-6.547), p=0.04]. Baseline serum CRP level was also associated with an elevated risk of all-cause mortality. Elevated baseline serum CRP levels elevated the risk of all-cause mortality by 6.6 % [HR 1.066 (1.031-1.103), $p<0.001$]. The univariate Cox regression analysis revealed that neither AIx nor PWV can predict all-cause mortality in SSc patients (Table IV).

Even after controlling for confounding factors such as lung involvement, predicted FEV1/

Table I. The baseline characteristics of the entire study population and comparison of baseline characteristics between alive and deceased patients.

	All patients (n=60)	Deceased (n=20)	Alive (n=40)	*p*-value
Age* (years)	49.1±12.3	55.6±9.8	45.8±12.4	0.003¶
Age of SSc onset* (years)	36.8±12.7	35.2±12.6	40±12.6	0.16¶
BMI* (kg/m²)	25.3±5.4	26.8±5.6	24.6±5.3	0.14¶
Women, *n* (%)	53 (88.3)	18 (90)	35 (87.5)	0.77§
Smoking status, *n* (%)				
Never	48 (80)	17 (85)	31 (77.5)	0.56§
Former	10 (16.7)	2 (10)	8 (20)	
Current	2 (3.3)	1 (5)	1 (2.5)	
Hypertension, *n* (%)	7 (10.3)	3 (15)	4 (10)	0.57§
Diabetes, *n* (%)	1 (1.5)	0 (0)	1 (2.5)	N/A
Hyperlipidemia, *n* (%)	22 (32.4)	8 (40)	14 (35)	0.7§
SBP* (mmHg)	118.5±21.2	123.5±28	116±16.8	0.19¶
DBP† (mmHg)	71.5 (70-80)	71 (61-87)	72.5 (70-80)	0.9‡
Limited scleroderma, *n* (%)	29 (48.3)	9 (45)	20 (50)	0.71§
Diffuse scleroderma, *n* (%)	31 (51.7)	11 (55)	20 (50)	0.71§
Reynaud phenomenon, *n* (%)	57 (95)	20 (100)	37 (92.5)	0.21§
Lung involvement, *n* (%)	27 (45)	13 (65)	14 (35)	0.03§
Skin involvement, *n* (%)	29 (48.3)	7 (35)	22 (55)	0.14§
Time from first Reynaud symptoms (yr)	11.5 (7-19)	18.5 (9-30)	11 (7-17)	0.03‡
Time from first non-Reynaud symptoms (yr)	9.5 (6-15.7)	11 (8-21)	9 (5.2-13)	0.07‡
FEV$_1$/FVC* (%, predicted)	81.5±9.2	78.2±11.4	83.2±7.5	0.045¶
DLCO* (%, predicted)	63.3±18.4	55.4±13.7	67.3±19.2	0.02¶
Autoantibodies, *n* (%)				
Anticentromere	13 (21.7)	6 (30)	7 (17.5)	0.27§
Anti-Scl-70	29 (48.3)	9 (45)	20 (50)	0.71§
Anti-U1-RNP	7 (11.7)	2 (10)	5 (12.5)	0.78§
Positive ANA	57 (95)	20 (100)	37 (92.5)	0.21§
Creatinine† (mg(dL)	0.6 (0.6-0.8)	0.65 (0.6-0.9)	0.6 (0.6-0.8)	0.65‡
eGFR	92.7±24.4	84.7±29.4	96.6±21	0.07¶
CRP†	3.6 (1.2-6.3)	5.5 (2.1-18.2)	3.3 (1.3-5.9)	0.04‡
Median follow-up time (yr)	10.3 (8.9-11.4)	6.2 (3.6-9.1)	10.8 (10.2-11.7)	<0.001

*: Mean ± std. deviation, †: Median (interquartile range). §Chi-square test, ‡Mann-Whitney U-test, ¶Student *t*-test. SSc; scleroderma, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, FEV1; forced expiratory volume, FVC; forced vital capacity, DLCO; carbon monoxide diffusing capacity of the lung, Anti-Scl-70; Anti-topoisomerase 1, Anti-U1-RNP; Anti-U1-Ribonucleoprotein, ANA; Anti-nuclear antibodies, eGFR; estimated Glomerular filtration rate, CRP; C-reactive protein.

FVC, predicted DLCO, and eGFR, multivariate Cox regression analysis indicated that elevated baseline serum CRP was an independent risk factor for all-cause mortality [HR 1.063 (1.027-1.100), *p*<0.001 (Table IV)].

Discussion

Our results showed that the overall survival rates in SSc patients were 98% at 1 year, 93% at 3 years, 88% at 5 years, and 68% at 10 years. Our results also showed that lung involvement predicted DLCO, eGFR, and baseline serum CRP were associated with poorer survival, and among these variables, baseline serum CRP was found to be an independent risk factor of all-cause mortality in SSc patients without PAH and obvious cardiac involvement. AS parameters, including AIx and PWV and echocardiographic variables, were not associated with all-cause mortality in our patient cohort.

The overall survival rates in our cohort were comparable with those previously reported[9-12]. In addition, we also demonstrated that lung involvement predicted DLCO, eGFR, and baseline serum CRP predicted all-cause mortality, which was consistent with already published data[9,12-15]. However, age at disease onset, male sex, diffuse scleroderma, predicted FEV1/FVC, and anti-Scl70 antibodies were not associated with all-cause mortality in our study population. The

Table II. Comparison of echocardiographic parameters between deceased and alive groups.

	Deceased (n=20)	Alive (n=40)	*p*-value
LVEDD* (mm)	42±4.4	42.3±5.1	0.8¶
LVESD* (mm)	24.4±3.2	24.8±3.5	0.6¶
LVEF† (%)	61.5 (60-66.5)	64 (60-68)	0.44‡
LV E/A†	0.91 (0.72-1.28)	1.2 (0.8-1.4)	0.11‡
LV EDT* (msn)	213±41.3	217±34.6	0.7¶
LV E/E'† ratio	8.8 (6.3-10.5)	7.8 (6.5-10)	0.34‡
LV Tei indeks† (%)	42 (34-52)	46 (40-57)	0.25‡
Left atrial area† (cm²)	16.6 (14.6-22)	16.7 (14.1-21)	0.7‡
RVd† (mm)	25 (24-27)	25 (23-27)	0.4‡
RV FAC† (%)	52 (50-57)	51 (46-59)	0.9‡
TAPSE† (mm)	21.5 (18-24)	21.5 (19-23)	0.86‡
RV S'† (cm/s)	15.8 (14.4-17.1)	16.2 (13.4-19)	0.71‡
RV Tei index† (%)	34 (27-48)	37.5 (28.5-49.5)	0.7‡
Right atrial area† (cm²)	14.3 (12.7-17)	13.3 (11.6-15.4)	0.14‡
SPAP† (mmHg)	29.5 (25-30)	28.5 (25-35)	0.6‡

*: Mean ± standard deviation, †: median (interquartile range). ‡Mann-Whitney U-test, ¶Student *t*-test. LVEDD; Left ventricular end-diastolic diameter, LVESD; Left ventricular end-systolic diameter, LVEF; Left ventricular ejection fraction, LV; Left ventricle, E; The early diastolic peak E wave, A; atrial contraction wave, EDT; E wave deceleration time, S'; Systolic velocity, RV; Right ventricle, E'; Diastolic velocity, FAC; Fractional area change, TAPSE; Tricuspid annular plane systolic excursion, SPAP; Systolic pulmonary artery pressure.

lack of significance could be attributed to an inadequate sample size used in our study.

The absence of prognostic significance of AS measures in all-cause mortality was the fundamental finding of our study. The pathogenesis and clinical symptoms of SSc are dominated by small vessel disease, but interest in large-vessel involvement, particularly atherosclerotic CVD, is growing. Several studies[16] have demonstrated that patients with autoimmune diseases have a greater risk of mortality, particularly from CV events. However, the risk of CV events, particu-larly atherosclerotic CV diseases, in patients with SSc is still unclear. Regardless of the technique, assessing subclinical atherosclerosis in SSc patients has not yielded consistent results in the past years. Nevertheless, the results of a recent meta-analysis[8] support the fact that macro-vascular abnormalities are substantially more prevalent in SSc patients with moderate to high inconsistency and significant heterogeneity in available data. The prognostic value of different AS parameters to predict CV and all-cause mortality in the literature is lacking. To our knowledge, this
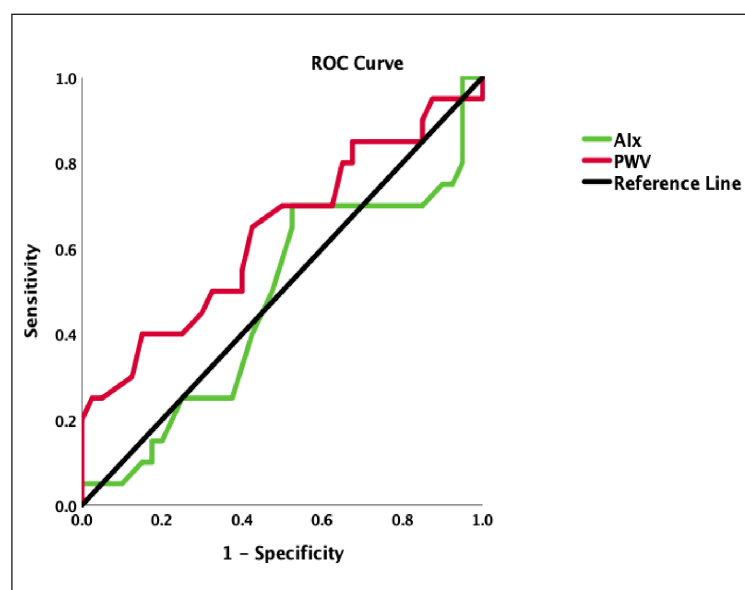

Figure 1. Receiver-operator-curve analysis of aortic pulse wave velocity (PWV) and augmentation index (AIx) for the prediction of all-cause mortality.

Table III. Comparison of arterial stiffness parameters between alive and deceased groups.

	Deceased (n=20)	Alive (n=40)	*p*-value
AIx[†] (%)	31.5 (26-39.5)	32 (25.5-36)	0.76[‡]
AoPWV[†] (m/sn)	5.5 (4.6-6.1)	5.9 (5.1-6.8)	0.09[‡]

[†]: median (interquartile range), [‡]Mann-Whitney U test. AIx; Augmentation index, AoPWV: Aortic pulse wave velocity.

report is the one that examined the prognostic value of AS parameters, which are the surrogate measures of CVD, in an SSc patient group over a long-term follow-up time of up to 10 years. Our results demonstrated that among AS parameters, neither AIx nor PWV can predict all-cause mortality in SSc patients.

Clinical studies[17,18] in the late '90s demonstrated that up to 20-25% of deaths in SSc patients were attributable to CV causes. However, acute myocardial infarction (AMI) constitutes 7.5% (n=12) of all deaths in the Danish cohort[18], in which the death information was mostly obtained from death certificates and medical records. Man et al[19] showed that the risk of stroke and MI was increased up to two-fold in SSc patients in comparison with control subjects [HR 2.61 (95% CI: 1.54-4.44) for stroke and HR 1.80 (95% CI: 10.7-3.05) for MI]. However, the elevated risk of CV events in this research was not fully attributed to atherosclerosis. The authors concluded that these events might be related to vasospasm, vasculitis, vasculopathy, and a mixture of atherosclerotic and non-atherosclerotic factors. Another study conducted by Ngian et al[20] demonstrated a 3.2-fold increase in patient self-report coronary heart disease in SSc patients compared with controls. Similarly, the etiology of coronary heart disease was not fully elucidated in this study.

In the Forth Universal definition[21] of MI, Type 1 MI refers to MI caused by plaque disruption with coronary athero-thrombosis, whereas Type 2 MI refers to MI caused by myocardial oxygen demand and supply mismatch irrelevant to acute coronary thrombosis. The etiology of Type 2 MI is multifactorial. Coronary vasospasm, coronary microvascular impairments including endothelial dysfunction, coronary embolism, or other reasons that reduce myocardial oxygen supply, including severe anemia and severe hypoxemia might result in Type 2 MI. Endothelial dysfunction is the primary immunologic and inflammatory disruption causing the typical extensive vasculopathy associated with SSc. Additionally, a key factor in the increased CV risk present in all systemic illnesses is the interaction between systemic inflammation, coagulation disturbances, autoimmune activation, and potential cardiotoxic effects of anti-rheumatic drugs[22]. Therefore, the increased risk of MI in patients with SSc might be partially explained by Type 2 MI rather than atherosclerotic plaque disruption, which might explain the inadequate prognostic value of AS variables in predicting mortality in our patient cohort.
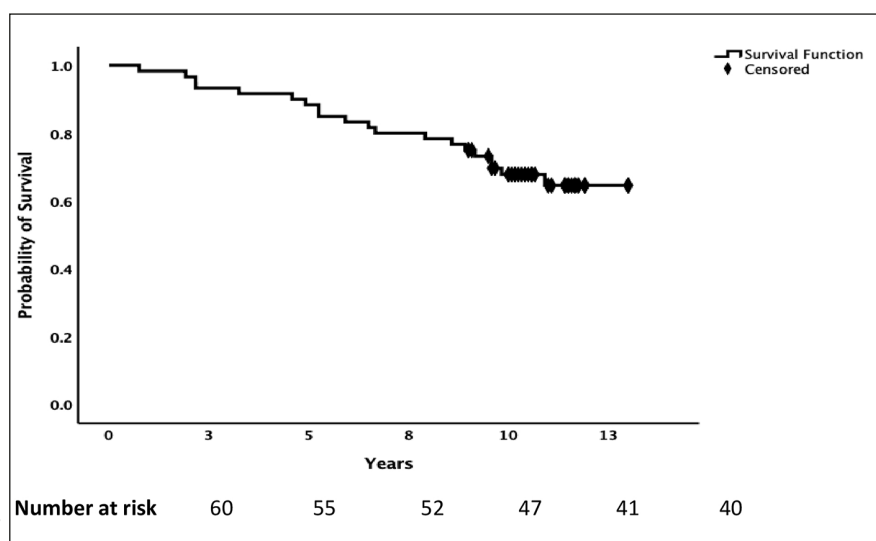

Figure 2. Kaplan-Meier analysis of overall survival.

Number at risk	60	55	52	47	41	40

Table IV. Univariate and multivariate Cox regression analysis for overall survival.

Variable	Univariate Cox regression analysis			Multivariate Cox regression analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age of SSc onset	1.026	0.991-1.063	0.14	-	-	-
Male sex	0.785	0.182-3.384	0.74	-	-	-
Diffuse subtype	1.143	0.474-2.759	0.77	-	-	-
Anti-Scl-70	0.852	0.353-2.057	0.72	-	-	-
Lung involvement	2.608	1.039-6.547	0.04	-	-	-
FEV1/FVC	0.957	0.914-1.002	0.06	-	-	-
DLCO	0.978	0.959-0.998	0.03	-	-	-
eGFR	0.979	0.960-0.999	0.04			
CRP	1.066	1.031-1.103	<0.001	1.063	1.027-1.100	<0.001
LVEF	0.962	0.889-1.042	0.34	-	-	-
LV E/E'	1.104	0.979-1.245	0.11	-	-	-
LV Tei index	0.986	0.960-1.013	0.31	-	-	-
TAPSE	0.992	0.877-1.122	0.9	-	-	-
RV S'	0.979	0.900-1.064	0.61	-	-	-
SPAP	0.968	0.885-1.058	0.47	-	-	-
RV Tei index	1.002	0.984-1.021	0.8	-	-	-
AIx	1.014	0.962-1.069	0.6	-	-	-
PWV	0.737	0.468-1.159	0.19	-	-	-

SSc; scleroderma, Anti-topoisomerase 1, Anti-U1-RNP; FEV_1; forced expiratory volume, FVC; forced vital capacity, DLCO; carbon monoxide diffusing capacity of the lung, Anti-Scl-70; Anti-topoisomerase 1, eGFR; estimated Glomerular filtration rate, CRP; C-reactive protein, LVEF; Left ventricular ejection fraction, LV; Left ventricle, E; The early diastolic peak E wave, E'; Diastolic velocity, S'; Systolic velocity, RV; Right ventricle, TAPSE; Tricuspid annular plane systolic excursion, SPAP; Systolic pulmonary artery pressure. AIx; Augmentation index, AoPWV: Aortic pulse wave velocity.

A recent study conducted by De Almeida Chaves et al[12] found that the majority of deaths (53.6%) in SSc were not related to the disease itself. CV mortality was found to be a major contributor to non-SSc-related mortality (37.8%). In this present study, sudden cardiac arrest constitutes 24.3%, MI constitutes 5.4%, and mesenteric ischemia constitutes 5.4% of cardiovascular deaths. However, there are several non-coronary causes of sudden cardiac death, including heart valve diseases, cardiomyopathy, carditis, conduction system abnormalities, pulmonary embolism, and malignant arrhythmias, which are already shown[23] to be present in patients with SSc. Hence, most deaths that have been attributed to CV mortality might not be related to atherosclerotic CV diseases. Our findings support this observation because we demonstrated that mortality in patients with SSc was a result of ongoing disease activation, as demonstrated by the independent predictive value of CRP. Cardiac manifestations in SSc can either be caused by the fibrotic processes that directly af-

fect all the structures of the heart or by secondary causes such as PAH, interstitial lung disease, or SSc renal crises[24,25]. Therefore, controlling disease activation rather than screening for atherosclerosis may represent a critical role in decreasing CV and all-cause mortality in SSc patients.

Previous reports[10-14] have demonstrated that cardiac involvement was an independent predictor of death in SSc patients. The definition of cardiac involvement varies between studies. Valvulopathy, pericardial effusion, low LVEF, and ECG abnormalities have been described as cardiac involvement. Our population consisted of patients without apparent cardiac involvement. We have searched whether occult cardiovascular involvement, which was examined by 2D echocardiography and TDI, could predict all-cause mortality. Detailed functional LV and RV parameters failed in predicting mortality in these patients. We excluded patients with ECG abnormalities and PAH therefore, our patient cohort might represent unique patients whose disease is in its

very early stages. Additionally, newer techniques, including global longitudinal strain, strain rate, and cardiac magnetic resonance (CMR) imaging, might detect occult cardiac involvement better than conventional 2D echocardiography and TDI.

Limitations

This study represents a single-center experience with a small number of SSc patients. We were unable to determine whether AS parameters had any predictive value for CV mortality and major adverse CV events. The echocardiographic data were limited to two-dimensional, PW, and TDI measurements and did not include more reliable speckle-tracking echocardiography and volumetric measurements. In addition, CMR offers important and promising results in terms of demonstrating both ventricular dysfunction and myocardial fibrosis in SSc patients[26]. Therefore, the lack of CMR imaging data in this study is another significant limitation. Finally, the lack of assessment of central AS may have affected our results. However, radial AIx was strongly correlated with carotid AIx in apparently healthy subjects, and radial AIx has a potential alternative marker of CV disease[27].

Conclusions

Our study demonstrated that peripheral AS parameters, including AIx and PWV, were not associated with all-cause mortality in SSc patients without PAH and obvious cardiac involvement. Additionally, baseline serum CRP was presented as an independent risk factor for mortality. Screening for surrogate measures of CV disease to decrease mortality in SSc patients might be time-consuming and not cost-effective. Therefore, controlling disease activation rather than screening for atherosclerosis may play a critical role in decreasing CV and all-cause mortality in SSc patients. Further large-scale research is required to better understand the exact mechanisms underlying CV deaths in SSc patients.

Conflict of Interest

None.

Funding

None.

Authors' Contributions

Dr. Ayşe Çolak took part in the design, analysis, interpretation, and drafting of the manuscript, Dr. Mehmet Emre Özpelit contributed to the analysis, interpretation, and review of the manuscript, Dr. Merih Birlik contributed to the diagnosis of scleroderma patients and review of the manuscript, and Dr. Ebru Özpelit took part in the arterial stiffness evaluation, echocardiographic examination and echocardiographic data analysis, design, interpretation and critical review of the manuscript.

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References

1) Denton CP, Khanna D. Systemic sclerosis. Lancet 2017; 390: 1685-1699.

2) van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA Jr, Carreira PE, Riemekasten G, Clements PJ, Denton CP, Distler O, Allanore Y, Furst DE, Gabrielli A, Mayes MD, van Laar JM, Seibold JR, Czirjak L, Steen VD, Inanc M, Kowal-Bielecka O, Müller-Ladner U, Valentini G, Veale DJ, Vonk MC, Walker UA, Chung L, Collier DH, Ellen Csuka M, Fessler BJ, Guiducci S, Herrick A, Hsu VM, Jimenez S, Kahaleh B, Merkel PA, Sierakowski S, Silver RM, Simms RW, Varga J, Pope JE. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/ European League against Rheumatism collaborative initiative. Ann Rheum Dis 2013; 72: 1747-1755.

3) Dimitroulas T, Giannakoulas G, Karvounis H, Settas L, Kitas GD. Systemic sclerosis-related pulmonary hypertension: unique characteristics and future treatment targets. Curr Pharm Des 2012; 18: 1457-1464.

4) Sandmeier B, Jäger VK, Nagy G, Carreira PE, Tzankov A, Widuchowska M, Antic M, Distler O,

Reichert H, Distler JH, Walker UA, Hügle T. Autopsy versus clinical findings in patients with systemic sclerosis in a case series from patients of the EUSTAR database. Clin Exp Rheumatol 2015; 33: 75-79.

5) Ross L, Prior D, Proudman S, Vacca A, Baron M, Nikpour M. Defining primary systemic sclerosis heart involvement: A scoping literature review. Semin Arthritis Rheum 2019; 48: 874-887.

6) Boueiz A, Mathai SC, Hummers LK, Hassoun PM. Cardiac complications of systemic sclerosis: recent progress in diagnosis. Curr Opin Rheumatol 2010; 22: 696-703.

7) Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55: 1318-1327.

8) Meiszterics Z, Tímár O, Gaszner B, Faludi R, Kehl D, Czirják L, Szűcs G, Komócsi A. Early morphologic and functional changes of atherosclerosis in systemic sclerosis-a systematic review and meta-analysis. Rheumatology (Oxford) 2016; 55: 2119-2130.

9) 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; 44: 208-219.

10) Pokeerbux MR, Giovannelli J, Dauchet L, Mouthon L, Agard C, Lega JC, Allanore Y, Jego P, Bienvenu B, Berthier S, Mekinian A, Hachulla E, Launay D. Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. Arthritis Res Ther 2019; 21: 86.

11) Ferri C, Sebastiani M, Lo Monaco A, Iudici M, Giuggioli D, Furini F, Manfredi A, Cuomo G, Spinella A, Colaci M, Govoni M, Valentini G. Systemic sclerosis evolution of disease pathomorphosis and survival. Our experience on Italian patients' population and review of the literature. Autoimmun Rev 2014; 13: 1026-1034.

12) De Almeida Chaves S, Porel T, Mounié M, Alric L, Astudillo L, Huart A, Lairez O, Michaud M, Prévot G, Ribes D, Sailler L, Gaches F, Adoue D, Pugnet G. Sine scleroderma, limited cutaneous, and diffused cutaneous systemic sclerosis survival and predictors of mortality. Arthritis Res Ther 2021; 23: 295.

13) Li X, Qian YQ, Liu N, Mu R, Zuo Y, Wang GC, Jia Y, Li ZG. Survival rate, causes of death, and risk factors in systemic sclerosis: a large cohort study. Clin Rheumatol 2018; 37: 3051-3056.

14) Panopoulos S, Bournia VK, Konstantonis G, Fragiadaki K, Sfikakis PP, Tektonidou MG. Predictors of morbidity and mortality in early systemic sclerosis: Long-term follow-up data from a single-centre inception cohort. Autoimmun Rev 2018; 17: 816-820.

15) Volkmann ER, Tashkin DP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L, Pinckney A, Furst DE, Clements PJ, Khanna D, Steen V, Schraufnagel DE, Arami S, Hsu V, Roth MD, Elashoff RM, Sullivan KM; SLS I and SLS II study groups. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. Ann Rheum Dis 2019; 78: 122-130.

16) Bartoloni Bocci E, Luccioli F, Angrisani C, Moscatelli S, Alunno A, Gerli R. Accelerated atherosclerosis in systemic lupus erythematosus and other connective tissue diseases. Expert Rev Clin Immunol 2007; 3: 531-541.

17) Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. Ann Rheum Dis 1998; 57: 682-686.

18) Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). Br J Rheumatol 1998; 37: 750-755.

19) Man A, Zhu Y, Zhang Y, Dubreuil M, Rho YH, Peloquin C, Simms RW, Choi HK. The risk of cardiovascular disease in systemic sclerosis: a population-based cohort study. Ann Rheum Dis 2013; 72: 1188-1193.

20) Ngian GS, Sahhar J, Proudman SM, Stevens W, Wicks IP, Van Doornum S. Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis. Ann Rheum Dis 2012; 71: 1980-1983.

21) Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 2018; 72: 2231-2264.

22) Zegkos T, Kitas G, Dimitroulas T. Cardiovascular risk in rheumatoid arthritis: assessment, management and next steps. Ther Adv Musculoskelet Dis 2016; 8: 86-101.

23) Markwerth P, Bajanowski T, Tzimas I, Dettmeyer R. Sudden cardiac death-update. Int J Legal Med 2021; 135: 483-495.

24) Parks JL, Taylor MH, Parks LP, Silver RM. Systemic sclerosis and the heart. Rheum Dis Clin North Am 2014; 40: 87-102.

25) Desai CS, Lee DC, Shah SJ. Systemic sclerosis and the heart: current diagnosis and management. Curr Opin Rheumatol 2011; 23: 545-554.

26) Agoston-Coldea L, Zlibut A, Revnic R, Florea M, Muntean L. Current advances in cardiac magnetic resonance imaging in systemic sclerosis. Eur Rev Med Pharmacol Sci 2021; 25: 3718-3736.

27) Sugawara J, Komine H, Hayashi K, Maeda S, Matsuda M. Relationship between augmentation index obtained from carotid and radial artery pressure waveforms. J Hypertens 2007; 25: 375-381.