Troponin elevation independently associates with mortality in systemic sclerosis

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Abstract

Objective

Cardiac involvement is common in systemic sclerosis (SSc), and elevated troponin may be the only sign of ongoing myocardial disease. The objective was to determine whether the presence of elevated troponin associates with unique SSc characteristics and poor outcomes.

Methods

This retrospective, cross-sectional study included patients in the Johns Hopkins Scleroderma Center Research Registry with any troponin measurement in the past 10 years. Clinical data were compared between those with elevated versus normal troponin. Survival analyses including Cox proportional hazards and regression analyses were performed.

Results

272 patients with a troponin measurement were identified. 83 (31%) had elevated troponin. Compared to those with a normal troponin level, those with elevated troponin level were more likely to have the diffuse SSc subtype (p=0.005), lower left ventricular ejection fraction (57.7 ± 20% vs. 64.4 ± 17.4%, p=0.007), lower forced vital capacity percent predicted (61.1 ± 18.8% vs. 66.8 ± 20.4%, p=0.03), higher right ventricular systolic pressure (51.4 ± 20.9 vs. 43.4 ± 15.9 mmHg, p=0.001), higher Medsger muscle and heart severity scores (p≤0.001), and higher frequency of mortality (28% vs. 9.5%, p≤0.0001). Patients with elevated troponin also have a 2.16-fold (95% CI 1.01-4.63, p=0.046) increased risk of death compared to those without elevated troponin even after adjusting for age, sex, disease duration, and cardiopulmonary risk factors.

Conclusion

Troponin may be a useful prognostic biomarker that may identify a subset of patients with heart disease that may warrant closer clinical investigation.

Key words

systemic sclerosis, cardiac disease, troponin

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Introduction

Cardiac disease in systemic sclerosis (SSc) is a significant contributor to morbidity and mortality. The prevalence of cardiac disease is broad and ranges from 7–45% based on the definition used to delineate the degree of cardiac complications (1, 2). While cardiac involvement is typically asymptomatic, when it becomes clinically evident, it has been reported to responsible for up to 30% of SSc-related mortality (3). A spectrum of cardiac abnormalities have been reported in scleroderma, ranging from inflammatory myocarditis, myocardial fibrosis, arrythmias, diastolic dysfunction, and chronic pericardial effusions (4). The lack of a standardised definition of heart involvement in scleroderma makes it challenging to accurately assess burden of cardiac disease and evaluate therapeutic strategies. Identification of clinically useful cardiac biomarkers can potentially provide clinicians with an easier method of detecting cardiac disease. Troponin has long been used to detect heart failure and myocardial ischaemia (5, 6). Cardiac troponin I is considered to be exclusive to the myocardial tissue, while troponin T has been reported to be detected in regenerating skeletal muscle tissue (7, 8). Furthermore, cardiac troponin I assays do not exhibit cross reactivity with skeletal muscle because cardiac troponin I has 31 additional amino acids in its assay compared with skeletal troponin I (9). It has also been reported to not exhibit cross-reactivity in patients with polymyositis or dermatomyositis, an important consideration when also examining the high risk association between skeletal and cardiac muscle disease in SSc (10, 11). The purpose of this study was to determine the clinical phenotype and risk of mortality of SSc patients who had an elevated troponin compared to those who did not have an elevated troponin.

Patients and methods

Utilising the prospective Johns Hopkins Scleroderma Center Research Registry, we queried our own institution's electronic medical record system to identify 272 registry participants who had a clinically obtained troponin I measurement in the last 10 years. Only those patients who consented to participate in the Registry were included. The Johns Hopkins Institutional Review Board approved this study. The Johns Hopkins Scleroderma Center Research Registry includes patients who meet the 2013 ACR/EULAR or the 1980 ACR criteria for SSc, have at least 3 of 5 features of CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias), or have all 3 of the following features: Raynaud's phenomenon, abnormal nailfold capillaries, and presence of a scleroderma specific antibody.

Clinical data up to the time of troponin measurement were also included. Key clinical variables included SSc disease subtype, age of SSc onset, disease duration, race, history of myopathy, and cardiopulmonary disease measures (defined below). Maximum and minimum values up to the time of troponin measurement were used to characterise the clinical phenotype of patients. Maximum values of the following variables were included to assess disease severity: modified Rodnan skin thickness score (mRSS), Medsger heart, kidney, lung, and muscle severity scores (12), World Health Organisation functional classification for pulmonary hypertension symptoms, pro-BNP, right ventricular systolic pressure (RVSP) on echocardiogram, creatine kinase, and aldolase. Minimum values of the following variables were included: lowest forced vital capacity (FVC) on pulmonary function tests (PFTs), diffusing capacity of lung for carbon monoxide (DLCO), ejection fraction on echocardiogram. History of myopathy was defined as proximal weakness and at least 1 abnormal diagnostic testing such as elevated CK, myopathic findings on electromyography (EMG), muscle oedema on muscle MRI, or biopsy evidence of myopathy. FVC and DLCO were standardised for sex and age (13, 14). The onset of scleroderma was defined by the date of the first non-Raynaud's phenomenon symptom attributable to scleroderma. Scleroderma disease severity measures were collected prospectively at 6-month intervals. Mortality data was

also obtained from the database and were verified by use of the Social Security Death Index.

Scleroderma specific autoantibodies were assayed on banked sera using a commercially available line immunoblot platform (Euroline Systemic Sclerosis Profile, EuroImmun Diagnostics, Lubeck, Germany) and only those with moderate or high positive titre were considered positive. Multicomponent autoantibody complex results such as PM/Scl, RNA polymerase III and Centromere were considered positive if either subunit (PM75 or 100, RP111 or 155, and centromere B or A) was moderate-high titre positive.

Co-morbid conditions were defined as follows: peripheral artery disease defined as history of ankle brachial index <0.9, history of claudication, history of amputation or ulceration due to peripheral macrovascular disease without any other clear explanation; coronary artery disease (CAD) defined as history of angina; abnormal standard exercise stress test, exercise/pharmacological stress imaging study or coronary angiogram, history of MI, or history of coronary revascularisation), and atherosclerotic cerebrovascular disease (ASCVD) defined as prior transient ischaemic attack or thrombotic or embolic stroke.

An elevated troponin-I was defined by any troponin-I >0.04 ng/mL (normal range: 0–0.4ng/mL) and used as the primary outcome in logistic regression analysis. Since renal failure has been associated with elevated troponin, patients with renal failure (n=14) defined as a Medsger kidney severity score ≥2 were excluded from this analysis, resulting in a total 217 patients who had available Medsger kidney severity score closest to the troponin assessment. We then used all-cause mortality as an outcome to determine which risk factors, including troponin, contributed to mortality.

Differences in clinical characteristics were compared between patients with an elevated troponin and those with normal troponin using student's *t*-tests and Fischer's exact test as appropriate. Distributions of Medsger severity scores were also compared using Kruskal-Wallis tests. Kaplan-Meier cumulative survival curves and time to cardiac event were computed to compares subjects with and without elevated troponin. Patients were classified as having a cardiac event if they developed arrhythmia, biventricular enlargement, LVEF(left ventricular ejection fraction)<45%, or clinical signs of heart failure. The log rank Mantel-Cox test was used to determine whether there were statistically significant differences in the survival and cardiac event rates of those with and without elevated troponin. Cox proportional hazards analyses were performed to determine the relationship between elevated troponin and survival, utilising scleroderma onset as the time origin of interest. Patients were censored by last visit date to the Center, death, or June 17, 2017, when this study dataset was closed. All statistical analyses were performed using Stata, version 17 (College Station, TX, USA). All statistical tests were 2-sided, and a *p*-value ≤0.05 was considered statistically significant.

Results

Clinical features of scleroderma patients with and without an elevated troponin

Of the 272 SSc patients found to have a troponin-I checked in our institution's electronic medical records, 83 (31%) had an elevated troponin (Table I). Those who had an elevated troponin had a mean value of 0.96±2.56 ng/mL vs. those who had a normal troponin was 0.03±0.01 ng/mL. There were no differences in age of scleroderma onset, sex, race, or disease duration between patients with and without elevated troponin. When compared to those without an elevated troponin, those with an elevated troponin were more commonly of the diffuse subtype (55% *vs.* 37%, *p*=0.005), had history of renal crisis (8.4% *vs.* 2.6%, *p*=0.05), and had a history of myopathy (51.8% *vs.* 30.2%, *p*=0.001). SSc patients with elevated troponin had more severe cardiopulmonary disease as demonstrated by higher maximum Medsger Heart Severity scores (defined as Heart Severity Score ≥2) (65.1% *vs.* 40.2%, *p*≤0.001) and lower ejection fraction (57.7%±19.9 *vs.* 64.4%±17.5, *p*=0.007). In fact, patients with elevated troponin had higher prevalence of severe cardiomyopathy with an EF of <35% (10.8% *vs.* 2.65%, *p*=0.008). Similarly, SSc patients with elevated troponin had higher maximum RVSP (51.4±20.9 mmHg *vs.* 43.4±15.9 mmHg, *p*=0.001) and a trend suggestive of more functional impairment (77.1% had maximum WHO dyspnoea Class 2 or greater *vs.* 66.7% of those who were troponin negative, *p*=0.08). Thirty-seven percent or 31 of 83 troponin positive patients had a right heart catheterisation, and 27 of the 31 (87.1%) had a mean pulmonary artery (PA) pressure >20 mmHg (15) which is considered to be diagnostic of pulmonary hypertension. The mean resting PA pressure was 26.5±11.4 and pulmonary capillary wedge pressure was 10.1±4.95 in those with elevated troponin. Those with elevated troponin also had more restrictive lung disease when compared to those without an elevated troponin (minimum FVC 61.1±18.8% *vs.* 66.8±20.4 %, *p*=0.03). Lastly, there was a higher frequency of mortality (28% *vs.* 9.5%, *p*0.0001) with a mean follow-up of 14.9±11.3 years from first non-Raynaud's symptom in those with elevated troponin. Troponin elevation was not associated with scleroderma autoantibody specificity or gastrointestinal, kidney, or Raynaud's severity as measured by the Medsger muscle severity scores. Amongst patients who died, it was notable that there was shorter mean time to death from troponin measurement by 1 year (1.06±1.02 years *vs.* 2.17±1.59 years, *p*=0.01). Furthermore, while comorbid conditions such as coronary artery disease and smoking were not statistically different between those with and without elevated troponin, other conditions such as peripheral artery disease was more frequent (14.6% *vs.* 4.4%, *p*=0.005).

Myopathy and cardiopulmonary disease associated withtroponin elevation

To determine whether specific scleroderma or cardiac characteristics were individually associated with elevated troponin, univariate logistic regression analyses were performed (Table II). The odds of having elevated tro-

Table I. Clinical characteristics of SSc patients with and without an elevated troponin.

Variable	Troponin positive (n=83)	Troponin negative (n=189)	*p*-value
Age at SSc onset, defined by 1st non-Raynaud's symptom, years (mean ± SD)	45.7 ± 14.2 years	43.9 ± 13.8 years	0.34
Female sex, no. (%)	60 (72.3%)	154 (81.5%)	0.108
Diffuse vs limited subtype, no. (%)	46 (55.4%)	70 (37%)	0.005
Disease duration at first visit, years (mean ± SD)	5.8 ± 8.5 years	6.1 ± 7.6 years	0.79
Disease duration at time of troponin measurement, years (mean ± SD)	10.4 ± 12.3 years	10.9 ± 9.7 years	0.70
African-American race vs other races, no. (%)	37 (44.6%)	66 (35%)	0.14
Baseline MRSS (mean ± SD)	11.5 ± 12.3	9.2 ± 10.0	0.10
History of Renal crisis, no. (%)	7 (8.4%)	5 (2.6%)	0.05
History of myopathy, no. (%)	43 (51.8%)	57 (30.2%)	0.001
Deceased by time of dataset closure, no. (%)	23 (27.7%)	18 (9.5%)	<0.0001
Time from Troponin Measurement to Death, (mean ± SD)	1.06 ± 1.02 years	2.17 ± 1.59 years	0.0105
Time from Troponin Measurement to dataset closure, (mean ± SD)	4.48 ± 7.36 years	4.28 ± 4.54 years	0.78
Time from first visit to Centre to Death, (mean ± SD)	7.52 ± 4.77 years	8.49 ± 4.51 years	0.52
Time from first visit to Centre to dataset closure, (mean ± SD)	9.04 ± 6.27 years	9.12 ± 6.08 years	0.92
Maximum RVSP, mmHg (mean ± SD)	51.4 ± 20.9	43.4 ± 15.9	0.001
Maximum pro-BNP, pg/mL (mean ± SD)	6205 ± 22110	897 ± 1834	0.003
Lowest ever EF, % (mean ± SD)	57.7 ± 9.9	64.4 ± 17.4	0.007
Ejection Fraction ≤35%, no. (%)	9 (10.8%)	5 (2.65%)	0.008
Ejection Fraction ≤50%, no. (%)	29 (34.9%)	23 (12.2%)	<0.001
Lowest FVC % predicted, (mean ± SD)	61.1 ± 18.8	66.8 ± 20.4	0.03
Max WHO ≥2, no. (%)	64 (77.1%)	126 (66.7%)	0.08
Maximum Medsger Heart Severity Score, no. (%)			0.001
0	25 (30.9%)	102 (55.1%)	
1	4 (4.9%)	11 (5.9%)	
2	10 (12.3%)	22 (11.9%)	
3	2 (2.5%)	5 (2.7%)	
4	40 (49.4%)	45 (24.3%)	
Maximum Medsger Heart Severity Score ≥2, no. (%)	54 (65.1%)	76 (40.2%)	<0.001
Maximum Medsger Muscle Severity Score ≥2, no. (%)	51 (61.5%)	66 (34.9%)	<0.001
Maximum Medsger Raynaud Severity Score ≥2, no. (%)	49 (59 %)	127 (67.2%)	0.22
Maximum Medsger GI Severity Score ≥2, no. (%)	25 (30.1%)	53 (28%)	0.77
Maximum Medsger Kidney Severity Score ≥2, no. (%)	11 (13.3%)	19 (10.1%)	0.53
Maximum Medsger Lung Severity Score ≥2, no. (%)	70 (84.3%)	140 (74.1%)	0.08
Comorbid Conditions, no. (%)			
Coronary Artery Disease	14 (17.1%)	21 (11.4%)	0.24
Ever Smoker	33 (39.8%)	76 (40.2%)	0.76
Dyslipidaemia	40 (48.8%)	63 (34.6%)	0.04
Diabetes	4 (4.88%)	11 (5.82%)	1.0
Peripheral artery disease	12 (14.6%)	8 (4.4%)	0.005
Atherosclerotic cardiovascular disease	9 (11%)	8 (4.3%)	0.06

The clinical characteristics (variables) in this table are based on clinical data up to the point of first troponin elevation. Disease duration was available in total n= 270, baseline MRSS and peripheral artery disease was available in n=266, time from Troponin measurement to death, n=40. Maximum RVSP and pro-BNP was available in total n=237, lowest ever EF was available in n=259, lowest FVC was available in n=260, coronary artery disease was available in total n=267, dyslipidaemia was available in total n=264, diabetes was available in 271, atherosclerotic cerebrovascular disease was present in 267. EBO autoantibody results for PM/Scl, RNA polymerase III and Centromere were considered positive if either subunit (PM75 or 100, RP111 or 155, and centromere B or A) was moderate-high titre positive. Follow-up Time from first visit to death was available in 40 patients (n=23 troponin positive, n=17 troponin negative). Follow-up time from first visit to dataset closure was available in 272 patients (n=83 troponin positive, n=189, troponin negative).

ponin was about 2 times higher if a SSc patient had diffuse scleroderma (OR 2.17 [95% CI 1.26–3.74], *p*=0.005) or dyslipidaemia (OR 1.88 [95% CI 1.09–3.27], *p*=0.02). Key cardiopulmonary parameters such as lowest ever EF demonstrated that for every one percent increase in the EF, there was a lower odd of having elevated troponin (OR 0.98 [95% CI 0.96–1.00], *p*=0.01). History of myopathy was also associated with 2.37 times higher odds of having elevated troponin (OR 2.37 [95% CI 1.37–4.10], *p*=0.002).

In multivariate analyses, history of myopathy (OR 3.10 [95% CI 1.47–6.55], *p*=0.003) and coronary artery disease (OR 2.94 [95% CI 1.10–7.91], *p*=0.03) were strongly associated with elevated troponin, even after controlling for all other cardiopulmonary and SSc confounders. Age of SSc onset (OR 1.03 [95% CI 1.00–1.07], *p*=0.04), lowest ever EF (OR 0.98 [95% CI 0.95–1.00], *p*=0.03), and maximum RVSP (OR 1.04 [95% CI 1.02–1.07], *p*<0.001) also associated with elevated troponin.

Troponin elevation and mortality

Troponin elevation was associated with increased risk for mortality in univariate Cox regression analyses [HR 2.71 [1.45–5.09], *p*=0.002 (Table III)]. Age of SSc onset was also associated with increased risk of death. For every additional year of patient age of SSc onset,

Table II. Examination of risk factors that preceded troponin elevation.

Variable	Unadjusted odds ratio [95% CI]	*p*-value	Adjusted odds ratio* [95% CI]	*p*-value
Age of SSc onset	1.01 [0.99-1.03]	0.36	1.03 [1.01-1.07]	0.04
Female sex	0.58 [0.31-1.09]	0.09	0.50 [0.22-1.14]	0.10
African-American race *vs*. other races	1.50 [0.87-2.57]	0.15	1.24 [0.56-2.72]	0.59
Diffuse *vs*. limited subtype	2.17 [1.26-3.74]	0.005	1.87 [0.85-4.11]	0.12
Disease duration	0.99 [0.96-1.03]	0.66	1.03 [0.98-1.08]	0.28
Coronary artery disease	1.73 [0.83- 3.61]	0.15	2.94 [1.10-7.91]	0.03
Dyslipidaemia	1.88 [1.09-3.27]	0.02	1.02 [0.50-2.13]	0.95
ASCVD	2.55 [0.92-7.08]	0.07	2.55 [0.75-8.74]	0.14
Renal crisis	1.83 [0.40 - 8.37]	0.44	0.93 [0.17 -5.06]	0.93
Lowest ever EF	0.98 [0.96 – 1.00]	0.01	0.98 [0.95 –1.00]	0.03
Maximum RVSP	1.02 [1.01- 1.04]	0.006	1.04 [1.02-1.07]	<0.001
Lowest FVC	0.98 [0.97-1.00]	0.006	1.00 [0.98-1.02]	0.95
Myopathy history	2.37 [1.37 – 4.10]	0.002	3.10 [1.50-6.55]	0.003

The risk factors (variables) noted in this table preceded or predated troponin elevation.
*Adjusted for age of SSc onset, sex, scleroderma disease subtype, race, disease duration, lowest ever EF, maximum RVSP, lowest FVC, hx of myopathy and the following cardiac risk factors: coronary artery disease, dyslipidaemia, ASCVD.

Table III. Cox proportional regression model for overall survival.

Variable	Unadjusted hazard ratio [95% CI]	*p*-value	Adjusted odds ratio [95% CI]	*p*-value
Elevated troponin	2.71 [1.45-5.09]	0.00	22.16 [1.01-4.63]	0.046
Age of SSc onset	1.07 [1.04-1.11]	<0.001	1.06 [1.02-1.09]	0.002
Female sex	0.72 [0.33-1.57]	0.41	0.66 [0.27-1.68]	0.38
African-American race vs other races	1.43 [0.75-2.72]	0.27	0.99 [0.37-2.68]	0.98
Diffuse subtype	2.47 [1.27-4.82]	0.008	1.23 [0.53-2.89]	0.63
Disease duration	0.89 [0.84-0.94]	<0.001	0.89 [0.83-0.95]	0.001
Coronary artery disease	0.53 [0.16-1.71]	0.29	0.56 [0.11-2.97]	0.50
Dyslipidaemia	0.64 [0.33-1.25]	0.20	0.76 [0.32-1/78]	0.52
ASCVD	1.09 [0.33-3.59]	0.88	1.11 [0.22-5.61]	0.89
Renal Crisis	0.75 [0.10-5.47]	0.78	1.02 [0.12-8.63]	0.50
Lowest EF	0.98 [0.96-1.00]	0.06	1.01 [0.98-1.04]	0.52
Myopathy	1.21 [0.62-2.40]	0.58	1.07 [0.44-2.59]	0.89
Maximum RVSP	1.01 [1.00- 1.03]	0.06	1.01 [0.98-1.03]	0.66
Lowest FVC	0.98 [0.97-1.00]	0.07	0.99 [0.96-1.01]	0.26

*Adjusted for age of SSc onset, sex, scleroderma disease subtype, race, disease duration, lowest ever EF, maximum RVSP, lowest FVC, hx of myopathy and the following cardiac risk factors: coronary artery disease, dyslipidaemia, ASCVD.

Table IV. Muscle characteristics of scleroderma patients with and without elevated troponin.

	Troponin positive (n=83)	Troponin negative (n=189)	*p*-value
Maximum Muscle Severity Score			
0	32 (38.6%)	123 (65.1%)	0.001
1	37 (44.6%)	48 (25.4%)	
2	10 (12.1%)	12 (6.4%)	
3	2 (2.4%)	2 (1.1%)	
4	2 (2.4%)	4 (2.1%)	
Abnormal EMG no. (%)	19 (22.9%)	20 (10.6%)	0.008
Muscle biopsy done, no. (%)	15 (18.1%)	17 (9%)	0.03
Muscle oedema on MRI, no. (%)	16 (19.3%)	17 (9%)	0.02
CK≥200, no. (%)	54 (65.9%)	57 (31.5%)	<0.001
Maximum CK ever, (mean ± SD)	514 ± 783	301 ± 553	0.01
Maximum aldolase, (mean ± SD)	15 ± 11	11.3 ± 6.3	0.003

EMG: electromyography; MRI: muscle magnetic resonance imaging; T2 STIR imaging to evaluate oedema. CK was available in n=263 patients, aldolase was available in n=200 patients, EMG was available in n=39 patients, muscle biopsy data was available in n=32, muscle MRI was available in n=33.

the risk of death increased by 7% (HR 1.07 [1.04–1.11], $p<0.001$). Patients who had diffuse SSc also had 2.47 times higher risk of death than those who did not have diffuse SSc (HR 2.47 [1.27–4.82], $p=0.008$).

In multivariate Cox proportional regression analyses, troponin elevation had an independent risk of death even after controlling for other confounding variables such as age at onset, sex, scleroderma disease subtype, race, disease duration, lowest ever EF, maximum RVSP, lowest FVC and other cardiac risk factors (HR 2.16 [1.01–4.63], $p=0.046$). In addition, age of SSc onset and disease duration continued to be risk factors for death. Diffuse SSc, renal crisis, myopathy, and lowest FVC did not associate with decreased survival in the adjusted model.

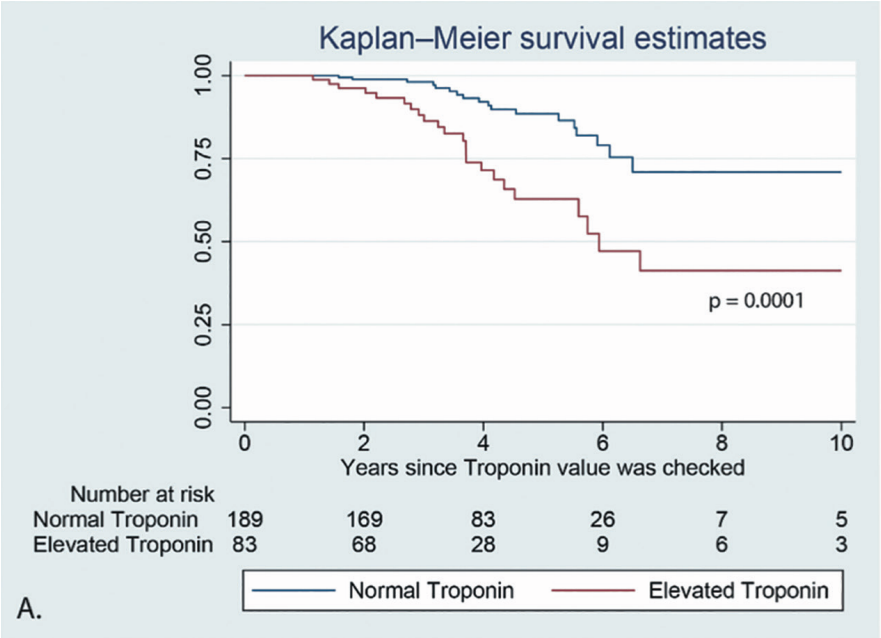
Kaplan-Meier cumulative survival curves were also generated for those with and without elevated troponin from the onset of first non-Raynaud's phenomenon and revealed that there was a statistically significant difference in the survival rate of these 2 groups ($p=0.0012$) (Fig. 1A).

Troponin elevation associates with shorter time to cardiac event

Cardiac event was defined as a Medsger cardiac severity score of ≥2 to capture LVEF <44% and heart failure or arrythmia (see methods) and modeled as an outcome. We found that in evaluating time to cardiac event after the measurement of troponin level, those with elevated troponin had a significantly shorter time to cardiac event ($p=0.001$) (Fig. 1B).

Other cardiac features of SSc patients with elevated troponin

EKGs were not routinely completed in all patients with elevated troponin, but in retrospective chart review of the 83 patients with troponin elevation, 77 had EKGs that were performed in our system. The data from EKGs, echocardiogram, and cardiac MRI were only used in this study if they were within 6 months before or at the time of troponin measurement. Thirty-eight of the 77 EKGs were abnormal (46%) as defined by any conduction abnormality.



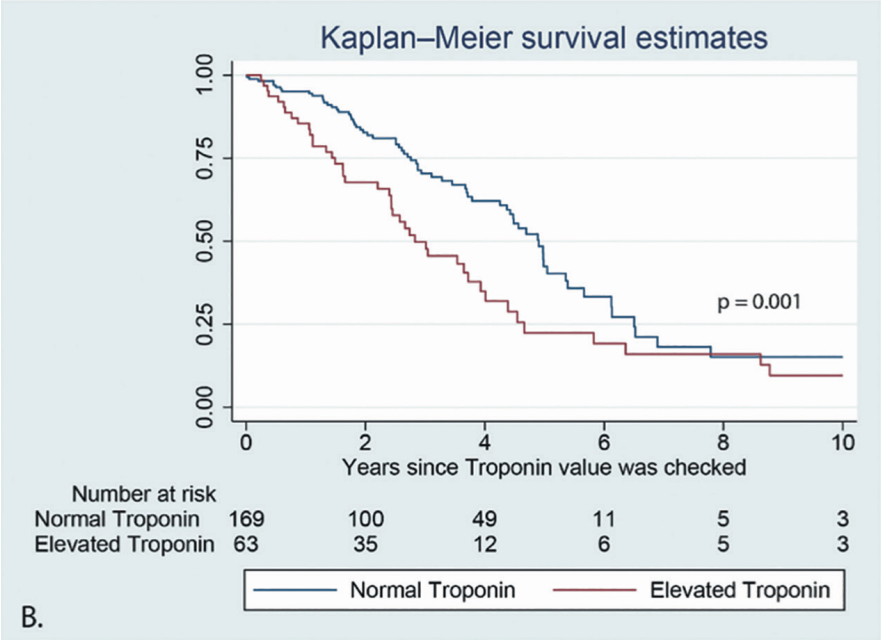


Fig. 1. A: Kaplan-Meier survival estimates comparing scleroderma patients who have elevated troponin *versus* those who have normal troponin and time till death.
B: Kaplan-Meier survival estimates comparing scleroderma patients who have elevated troponin *versus* those who have normal troponin and time till cardiac event.

More specifically, of the 38 abnormal EKGs, 8 had atrial fibrillation/flutter, 11 had right bundle branch block, 12 had left bundle branch block or fascicular block, 3 with first degree block, 1 with complete heart block, 1 with frequent PVCs, 1 with T-wave inversions. A total of 12 out of 83 patients (14%) had a cardiac MRI completed. Ten out of 12 (83.3%) had delayed enhancement suggesting myocarditis.

Muscle characteristics of SSc patients with elevated troponin

In SSc patients with an elevated troponin, 43 of 83 (52%) patients had a myopathy as defined by proximal weakness and at least one abnormal test to include elevated muscle enzymes, myopathic findings on EMG, muscle oedema on muscle MRI, and abnormal muscle biopsy. Patients with elevated troponin also had higher CK values (514±783 *vs.* 301±553, p=0.01) and higher aldolase levels (15±11 *vs.* 11.3±6.3, p=0.002) (Table IV). Of the 17 patients who had a muscle biopsy, 9 had a necrotising myopathy, 1 had dermatomyositis, 2 had fibrosing myopathy, 2 had non-specific myositis, 1 with normal muscle biopsy, and 1 biopsy with mitochondrial changes. Of the 21 patients who had an EMG, 10 had an irritable myopathy, 9 had a non-irritable myopathy, 1 normal EMG, 1 was only recorded as abnormal. One patient had an endomyocardial biopsy with evidence of fibrosis.

Discussion

This retrospective cross-sectional study of well-phenotyped scleroderma patients was undertaken to determine whether the presence of elevated troponin was associated with unique SSc characteristics and whether it was associated with poor outcomes such as mortality. We found that scleroderma patients with elevated troponin tend to have diffuse scleroderma with more severe cardiopulmonary disease as measured by lower FVC and ejection fraction and higher RVSP on echocardiogram with elevated pro-BNP. History of myopathy as defined by proximal weakness with at least one abnormal diagnostic test such as elevated muscle enzymes, myopathic EMG, muscle oedema on muscle MRI, and myopathic findings on muscle biopsy was also clearly associated with the presence of troponin elevation. Both univariate and multivariate analyses demonstrated that cardiopulmonary disease and myopathy predicted troponin elevation even after controlling for potential confounders such as age, sex, race, disease duration, SSc subtype, and cardiac risk factors. In contrast, only troponin elevation (up to 2.7-fold higher odds), age of SSc onset, and disease duration predicted mortality in Cox regression analyses in both univariate and multivariate analyses.

Survival analysis demonstrated that those with elevated troponin had lower survival rates and higher rate of cardiac events as defined by development of arrhythmia, biventricular enlargement, LVEF<45%, or clinical signs of heart failure. Furthermore, it was found that time to death from the troponin assess-

ment was 1.06±1.02 years *vs*. 2.16±1.59 years (p=0.01). While this time interval is short, it also highlights the bias of the study that may have selected for more severely ill patients that prompted the providers to check a troponin level. The notion that these SSc patients may have had more cardiac dysfunction that led to decreased survival is further supported in those cases with available data that showed EKG evidence of arrythmias such as heart block and atrial fibrillation and/or oedema on cardiac MRI suggesting myocarditis.

The definition of heart involvement in scleroderma is heterogeneous but it is unequivocal that it portends poor prognosis (16). Identification of biomarkers, such as cardiac troponin is an attractive measurement of cardiac disease because it is a simple and reproducible test that can also be followed prospectively. Troponin I is commonly used in clinical practice to diagnose myocardial ischaemia and is the most specific in detecting myocardial inflammation of the different troponin subunits. Troponin elevation in SSc is thought to be related to microvascular reperfusion injury which is in contrast to epicardial coronary disease seen in other non-SSc populations (11). It is reported that troponin I has 90% sensitivity for MI 8 hours after onset of symptoms and 95% specificity (17). A recent study by Bossello *et al*. (18) in 2019 also assessed the clinical features of a large group of SSc patients with elevated troponin and compared them to those who did not have an elevated troponin. They found that elevated troponin supported the presence of heart involvement and skeletal myositis. This finding was corroborated by our current study in that we found elevated troponin was associated with severe cardiopulmonary disease such as restrictive lung disease, cardiomyopathy (EF<35%), and muscle involvement. Unlike our retrospective study however, Bossello *et al*. prospectively collected troponin T levels instead of troponin I. While cardiac troponin I is reported to be more specific in discriminating skeletal vs. myocardial inflammation (19, 20), it is interesting to note that there was significant overlap in patients having both cardiac and skeletal muscle inflammation suggesting shared disease mechanisms/pathogenesis.

Barsotti *et al*. also evaluated whether both high sensitivity cardiac troponin T and NT-proBNP might be a useful marker of subclinical heart involvement in SSc (3). The reason for using NT-proBNP was because it has been reported to be reliable marker in the detection of primary cardiac involvement in prior studies (21, 22). Interestingly, Barsotti and colleagues determined that cardiac troponin T may be more specific than NT-proBNP for heart dysfunction. In our study, while we retrospectively obtained pro-BNP levels, they were not used in our multivariate logistic analyses because it was not associated with our primary outcome of interest of all-cause mortality. However, we believe this lack of association may be due to the discordance in the timing of the troponin elevation to the maximum pro-BNP levels ever obtained in our study.

The limitations of this study are the retrospective design and the convenience sampling of the patients in this study. Since troponin was not uniformly collected for all patients entering the scleroderma cohort, we used our institutional electronic medical records to identify patients who have had a troponin value ever checked by a provider. A reason for troponin determination was not captured in our registry. Therefore, our study is limited by sampling bias and our comparator group (measured, but normal troponin) may not be representative of the scleroderma population at large and we may be missing another group of asymptomatic patients who may have troponin elevation. All patients who have a measured troponin are likely to have more cardiopulmonary disease compared to those where troponin was not measured. Another limitation is lack of prospective, objective advanced cardiac testing such as cardiac MRIs in our study. Cardiac MRIs has recently been shown to play an important role in the detection of cardiac disease even in the absence of abnormalities on echocardiography (23), therefore this imaging technique may be a highly valuable tool to understand the aetiology and impact of troponin elevation.

In conclusion, our study highlights the importance of troponin elevation being associated with more severe cardiopulmonary disease and worse survival even after controlling for potential confounders. We feel that this is clinically relevant and demonstrates the potential future utility of using troponin as a biomarker of underlying cardiopulmonary disease that is easy to test and re-test in a clinical setting. Future studies of long-term follow-up and standardised cardiac assessment will be required to fully gain an understanding and appreciation of troponin as a cardiac biomarker in scleroderma.

Take home messages

- SSc patients with elevated troponin are more likely to have more severe cardiopulmonary disease, diffuse scleroderma, and concomitant myopathy.
- Elevated troponin was associated with increased all-cause mortality even after controlling for demographic and disease specific confounders.
- Troponin may be a potential biomarker in the study of primary cardiac manifestations in SSc and may identify SSc patients with more severe systemic disease.

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