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NT-proBNP, hs-cTnT, and CRP predict the risk of cardiopulmonary outcomes in systemic sclerosis: Findings from the Canadian Scleroderma Research Group

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Abstract

Objective: The aim of this study was to determine the independent value of N-terminal pro b-type natriuretic peptide, high-sensitivity cardiac troponin T, and C-reactive protein to predict onset of cardiopulmonary disease in a large, multicenter systemic sclerosis cohort followed prospectively.

Methods: Subjects from the Canadian Scleroderma Research Group registry with data on N-terminal pro b-type natriuretic peptide, high-sensitivity cardiac troponin T, and C-reactive protein were identified. Outcomes of interest were death, systolic dysfunction (left ventricular ejection fraction $< 50\%$ or medications for heart failure), pulmonary arterial hypertension by right heart catheterization, pulmonary hypertension by cardiac echocardiography (systolic pulmonary artery pressures $\geqslant 45$ mmHg), arrhythmias (pacemaker/implantable cardiac defibrillator or anti-arrhythmic medications), and interstitial lung disease. Multivariate Cox proportional hazard models were generated for each outcome.

Results: A total of 675 subjects were included with a mean follow-up of 3.0 ± 1.8 years. Subjects were predominantly women (88.4%) with mean age of 58.2 ± 11.3 years and mean disease duration of 13.7 ± 9.1 years. One hundred and one (101, 15%) subjects died during follow-up, 37 (6.4 %) developed systolic dysfunction, 18 (2.9%) arrhythmias, 34 (5.1%) pulmonary arterial hypertension, 43 (7.3%) pulmonary hypertension, and 48 (12.3%) interstitial lung disease. In multivariate analyses, elevated levels of N-terminal pro b-type natriuretic peptide, high-sensitivity cardiac troponin T, and C-reactive protein were associated with increased risk of death, while elevated levels of N-terminal pro b-type natriuretic peptide and C-reactive protein were associated with increased risk of developing pulmonary hypertension.

Conclusion: In systemic sclerosis, N-terminal pro b-type natriuretic peptide, high-sensitivity cardiac troponin T, and C-reactive protein have independent predictive value for death and pulmonary hypertension. A larger study would be required to determine the predictive value of these biomarkers for less common systemic sclerosis outcomes.

Keywords

NT-proBNP, hs-cTnT, CRP, cardiopulmonary outcomes, pulmonary arterial hypertension

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by vasculopathy, autoimmunity, and fibrosis. Cardiopulmonary disease is the principal cause of mortality in SSc.[1,2] Lung involvement in SSc is mostly due to interstitial lung disease or pulmonary arterial hypertension (PAH).[3,4] Cardiac abnormalities in SSc include myocardial and pericardial disease, as well as conduction abnormalities.[5,6]

Early detection of pulmonary and cardiac involvement are important goals in the management of the disease. Although high-resolution computed tomography (HRCT) scans of the lung are the gold standard for the detection of interstitial lung disease (ILD), the risks of radiation and

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costs preclude it from being a regular screening tool. Current guidelines recommend screening SSc patients with yearly echocardiography to detect PAH. However, the echocardiogram can both over- and under-estimate pulmonary artery systolic pressure.[7–9] The cost effectiveness of this strategy is also unknown.[10] Evidence-based guidelines to detect primary cardiac involvement are not well established.[11] Thus, novel biomarkers are needed in the pre-clinical detection of lung and cardiac complications of SSc.

N-terminal pro b-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), and C-reactive protein (CRP) have emerged as potential biomarkers of cardiac and lung disease in SSc, although the data is still limited. Higher levels of NT-proBNP were reported to be associated with both cardiac disease and PAH in SSc patients.[12–14] Similarly, studies have shown that, compared to the general population, patients with SSc have higher levels of hs-cTnT, and this correlates with the presence of scleroderma heart disease.[15,16] CRP is also elevated in some patients with SSc and this correlates with disease severity and lung involvement.[17]

Nevertheless, studies to date are limited by small, selected cohorts, cross-sectional study designs, and lack of data regarding the ability of these biomarkers to predict the onset rather than the presence of established cardiac and lung disease. Thus, the aim of this study was to measure NT-proBNP, hs-cTnT, and CRP in a large, unselected SSc cohort free of cardiopulmonary disease and followed prospectively in order to test the ability of these biomarkers to predict onset of cardiopulmonary disease. This could inform the development of evidence-based screening tools for cardiac and lung involvement in SSc.

Methods

Study population

Patients included in this study were from the Canadian Scleroderma Research Group (CSRG) Registry, a multicentre cohort followed annually since 2004. Ethics committee approval for this study was obtained at the Jewish General Hospital (Montreal, Canada) and at all participating CSRG sites. All subjects provided written informed consent.

Patients in the CSRG cohort must have a diagnosis of SSc confirmed by a rheumatologist, be $\geqslant$18 years of age, and likely to be compliant with study procedures and visits. Over 98% of subjects in the cohort meet the 2013 ACR/EULAR classification criteria for SSc.[18] This study included patients recruited between cohort inception and June 2015.

Predictor variables

Sera were collected at baseline and annual registry visits using standard operating procedures and aliquots stored in a central lab at the University of Calgary at −80°C. For the purposes of this study, an aliquot of the sera was thawed and analyzed to measure NT-proBNP and hs-cTnT. NT-proBNP was measured on a Roche Elecsys proBNP II analyzer and hs-cTnT was measured on a Roche Elecsys TnT hs STAT analyzer. CRP was measured in local laboratories and results recorded in the CSRG database.

Outcome variables

The outcomes of interest in this study were death, systolic dysfunction, PAH, PH, arrhythmias, and ILD. Death was recorded at the time of missed annual study visits and the date and cause of death verified with study physicians and next of kin. Transthoracic echocardiograms (TTE) were performed by local cardiologists to measure left ventricular ejection fraction (LVEF) and systolic pulmonary artery pressure (SPAP). For this study, systolic dysfunction was defined as LVEF $<$ 50% or use of heart failure medications as recorded by study physicians.[19] Mild systolic dysfunction was defined as LVEF from 45% to 49%, moderate as LVEF from 40% to 44%, and severe as LVEF $<$ 40%. PAH was defined as mean pulmonary artery pressure (mPAP) $\geqslant$ 25 and pulmonary capillary wedge pressure (PCWP) $\leqslant$ 15 on right heart catheterization. PH was defined as SPAP $\geqslant$ 45 mmHg measured by TTE (an estimate that correlates strongly with the values reported in right-sided heart catheter studies)[20] and no PAH, although not everyone with PH underwent a right heart catheterization, including those with another explanation for PH such as moderate to severe ILD or left heart disease. Arrhythmias were defined as either use of anti-arrhythmic medications (as recorded by a study physician) or presence of pacemaker and/or implantable cardiac defibrillator. The presence of ILD was determined using a published clinical decision rule.[21] This algorithm considers ILD to be present if a HRCT scan of the lung was interpreted by a radiologist as showing ILD or, in the case where no HRCT is available, if either a chest X-ray was reported as showing increased interstitial markings (not thought to be due to congestive heart failure) or fibrosis, and/or if a study physician reported the presence of typical "velcro-like crackles" on physical examination.

Covariates

Demographic variables (age, sex, race/ethnicity), smoking history, and comorbidities were self-reported by study subjects. Height and weight were extracted from the pulmonary function test reports. Disease duration was recorded by study physicians from the date of onset of Raynaud's phenomenon and from the date of onset of the first non-Raynaud's symptom attributable to SSc. Skin involvement was measured using the modified Rodnan skin score,[22] and patients were classified into diffuse (involvement of

proximal limbs and/or trunk) or limited (involvement of distal limbs and/or face) cutaneous subsets. Patients completed the Scleroderma Health Assessment Questionnaire (S-HAQ) and its visual analogue scales, including for dyspnea (range of 0–10, with 0 being no limitation and 10 being very severe limitation). Gastrointestinal (GI) involvement was measured by a questionnaire of 14 symptoms (GI-14) answered as yes or no. History of scleroderma renal crisis, inflammatory myositis, and inflammatory arthritis were recorded by the study physician.

Pulmonary function tests were performed in local respiratory physiology laboratories and data on forced vital capacity (FVC) and diffusion capacity of the lungs for carbon monoxide (DLCO) were extracted from reports. DLCO was corrected for hemoglobin.

Autoantibody analyses were performed on sera collected at the baseline study visit by Mitogen Diagnostics Laboratory, University of Calgary. Anti-centromere (CENP-A and CENP-B; ACA), anti-topoisomerase 1 (ATA), and anti-RNA polymerase III (RP11 and RP155; ARNAP) autoantibodies were detected by Euroline systemic sclerosis profile line immunoassay (Euroimmun GmbH, Luebeck, Germany) according to manufacturer's instructions. Autoantibodies were reported as absent (negative, equivocal, and low titers) and present (moderate and high titers).

Statistical analysis

Characteristics of the study population were summarized using descriptive statistics. Continuous variables were presented as means ± standard deviations. Categorical variables were expressed as frequencies and percentages. Characteristics of the patients according to the presence or absence of the outcomes of interest were similarly analyzed. For these analyses, patients who already had a diagnosis of the outcome of interest were excluded from the group. For example, patients who already had a diagnosis of systolic dysfunction at the time of their inclusion in the CSRG registry were excluded from the analyses for that outcome.

Univariate comparisons were performed using Student's t-test and Wilcoxon–Mann–Whitney U test to compare continuous variables, and chi-square test and Fisher exact test for categorical variables. Multivariate analyses were carried out using Cox proportional hazard models. NT-proBNP, hs-cTnT, and CRP were analyzed as continuous variables. Since the distributions of NT-proBNP, hs-cTnT, and CRP were left skewed, the logarithmic values to the base of 2 were used. Thus, a doubling in the value of the biomarker of interest is equal to a log2 fold change of 1, a quadrupling is equal to a log2 fold change of 2, and so on. Multivariate models for arrhythmia could not be constructed because the number of events (n = 18) was too small. To investigate the independent and combined effects of NT-proBNP, hs-cTnT, and CRP, eight separate models were generated: model **a** was the multivariate model without any of the three predictors; model **b** was model **a** with NT-proBNP; model **c** was model **a** with hs-cTNT; model **d** was model **a** with CRP; model **e** was model **a** with both NT-proBNP and hs-cTnT; model **f** was model **a** with both NT-proBNP and CRP; model **g** was model **a** with hs-cTnT and CRP; and model **h** was model **a** with NT-proBNP, hs-cTnT, and CRP. Model fit was interpreted using the Akaike information criterion (AIC), C statistics, and C statistics after cross-validation.

Models were fit using multiple imputation to include all subjects. Missing data were imputed 50 times using *mice* package and Cox models were fit with *survival* package in R version 3.5.1 for Windows (http://r-project.org). Numeric variables were imputed by predictive mean matching approach and binary variables were imputed by logistic regression. A two-step procedure for variable selection with the multiple imputed data was performed. A stepwise selection was first performed with all the covariates in each of 50 imputed datasets separately, which ended up with 50 different selection models. The frequency that each covariate appeared in these models was counted. Variables that appeared in at least 25 models were preselected. All the pre-selected covariates from the first step were then entered into an alternative model. A reduced model was defined by excluding the covariates that appeared the least times. The multivariate Wald statistic calculated from 50 imputed datasets was used to compare the goodness of fit of the reduced model against the alternative model.[23] This procedure was repeated until none of the covariates could be removed from the final model. The assumption of proportional hazards was verified for all models.

Results

Study population

A total of 675 patients were included in this study (Table 1). The mean age was 58.2 ± 11.3 years and 88.4% were females. The mean duration of disease from the onset of Raynaud's symptom was 17.7 ± 12 years, and from the onset of first non-Raynaud's symptom was 13.7 ± 9.1 years. Almost half of the subjects (44.6%) had diffuse cutaneous SSc. All of the 675 patients were included in the analysis for death, 576 for systolic dysfunction, 675 for PAH, 586 for PH, 627 for arrhythmias, and 389 for interstitial lung disease.

Serum level of biomarkers

The majority of patients (n = 403, 60%) had normal NT-proBNP, hs-cTnT, and CRP, while 158 (23.4%) had abnormal hs-cTnT, 127 (18.8%) abnormal CRP, and 108 (16.0%) abnormal NT-proBNP.

Table 1. Characteristics of the study population.

	Whole group (N = 675)		Normal hs-cTnT, NT-proBNP, and CRP (N = 403)	Abnormal hs-cTnT (N = 158)	Abnormal NT-proBNP (N = 108)	Abnormal CRP (N = 127)
	Mean (SD) or N (%)	# of missing	Mean (SD) or N (%)	Mean (SD) or N (%)	Mean (SD) or N (%)	Mean (SD) or N (%)
Age, years	58.2 (11.3)	0	58.0 (10.7)	61.5 (12.7)	58.7 (11.9)	57.3 (11.9)
Female	597 (88.4%)	0	365 (90.6%)	135 (85.4%)	84 (77.8%)	112 (88.2%)
White	592 (90.5%)	21	360 (91.6%)	142 (92.8%)	94 (88.7%)	110 (88.7%)
Cardiovascular risk factors						
Smoking (ever)	397 (59.3%)	6	244 (61.0%)	88 (56.1%)	57 (52.8%)	81 (64.3%)
Hypertension	253 (37.5%)	1	133 (33.0%)	72 (45.9%)	60 (55.6%)	48 (37.8%)
Diabetes	53 (7.9%)	5	21 (5.3%)	20 (12.7%)	15 (13.9%)	16 (12.6%)
BMI $> 30\,kg/m^2$	113 (17.1%)	14	65 (16.5%)	18 (11.5%)	15 (13.9%)	29 (23.6%)
Comorbidities						
Myocardial infarction	40 (6.0%)	5	12 (3.0%)	22 (14.0%)	9 (8.3%)	7 (5.5%)
Congestive heart failure	71 (10.6%)	5	26 (6.5%)	33 (21.0%)	26 (24.1%)	15 (11.8%)
Peripheral vascular disease	24 (3.6%)	5	10 (2.5%)	8 (5.1%)	7 (6.5%)	4 (3.2%)
Cerebrovascular accident	34 (5.1%)	5	15 (3.8%)	13 (8.3%)	8 (7.4%)	7 (5.5%)
Disease duration, years						
From first NR (non-Raynaud's) symptom	13.7 (9.1)	0	13.7 (9.3)	11.8 (8.7)	15.1 (9.2)	13.8 (8.9)
From onset of RP (Raynaud's phenomenon)	17.7 (12.0)	11	18.0 (11.8)	15.0 (11.8)	19.4 (12.3)	17.8 (12.1)
Modified Rodnan Skin Score	8.3 (8.6)	14	6.9 (7.2)	12.4 (12.6)	10.1 (9.8)	10.7 (9.8)
Diffuse cutaneous SSc	301 (44.6%)	0	160 (39.7%)	80 (50.6%)	62 (57.4%)	64 (50.4%)
Scleroderma renal crisis	27 (4.0%)	5	10 (2.5%)	10 (9.3%)	12 (7.6%)	7 (5.5%)
Shortness of breath (0–10)		44				
Median, [Q1, Q3]	1.0 [0, 3.0]		1.0 [0, 2.0]	2.0 [0, 6.0]	8.0 [2.5, 14.0]	1.0 [0, 5.0]
FVC, %predicted	91.8 (19.0)	108	96.9 (17.7)	82.1 (20.2)	82.4 (18.4)	82.6 (18.5)
DLCO, %predicted	69.0 (21.4)	141	73.8 (21.0)	56.9 (19.1)	58.0 (18.7)	62.5 (19.7)
SPAP, mmHg	34.8 (15.7)	276	31.2 (11.3)	43.5 (18.6)	44.9 (23.0)	39.6 (17.2)
Inflammatory myositis	40 (6.0%)	4	17 (4.3%)	14 (8.9%)	14 (13.0%)	9 (7.1%)
Inflammatory arthritis	108 (16.2%)	8	59 (14.8%)	30 (19.4%)	15 (14.0%)	22 (17.6%)
GI-14		44				
Median, [Q1, Q3]	2.0 [1.0, 5.0]		2.0 [1.0, 4.0]	3.0 [1.0, 5.0]	3.0 [1.0, 5.0]	3.0 [1.0, 5.0]
Digital ulcers	242 (36.1%)	4	136 (34.0%)	65 (41.4%)	48 (44.4%)	49 (38.9%)
Antibodies		49				
Anti-centromere	246 (39.3%)		162 (43.8%)	54 (36.0%)	28 (27.7%)	38 (31.9%)
Anti-topoisomerase I	97 (15.5%)		47 (12.7%)	32 (21.3%)	22 (21.8%)	22 (18.5%)
Anti-RNA polymerase III	92 (14.7%)		54 (14.6%)	19 (12.7%)	18 (17.8%)	20 (16.8%)
Follow-up time, years	3.0 (1.8)	0	2.9 (1.8)	3.1 (1.7)	3.2 (1.8)	3.0 (1.7)
Mortality	101 (15.0%)	0	32 (7.9%)	43 (27.2%)	37 (34.3%)	30 (23.6%)
Pulmonary arterial hypertension, ever	0	0	0	0	0	0
Pulmonary hypertension, ever	89 (13.3%)	7	26 (6.5%)	41 (26.3%)	32 (29.6%)	25 (20.0%)
Arrhythmias	48 (7.1%)	0	17 (4.2%)	28 (17.7%)	16 (14.8%)	10 (7.9%)
Pacemaker, ever*	8 (1.3%)		4 (1.1%)	4 (2.8%)	4 (4.2%)	1 (0.9%)
Anti-arrhythmic medications	41 (6.1%)		13 (3.2%)	25 (15.8%)	13 (12.0%)	10 (7.9%)
Left ventricular ejection fraction		135				
Normal	517 (95.7%)		328 (98.2%)	115 (91.3%)	73 (86.9%)	86 (96.6%)
Mildly decreased (<50%)	11 (2.1%)		3 (0.9%)	3 (2.4%)	5 (5.9%)	3 (3.4%)
Moderately decreased (<45%)	4 (0.7%)		2 (0.6%)	2 (1.6%)	0	0
Severely decreased (<40%)	8 (1.5%)		1 (0.3%)	6 (4.7%)	6 (7.2%)	0
Interstitial lung disease	281 (42.1%)	7	1 35 (33.9%)	80 (51.3%)	58 (53.7%)	75 (59.1%)

hs-cTnT: high-sensitivity cardiac troponin T; NT-proBNP: N-terminal pro b-type natriuretic peptide; CRP: C-reactive protein; SD: standard deviation; BMI: body mass index; FVC: forced vital capacity; DLCO: diffusion capacity of the lungs for carbon monoxide; SPAP: systolic pulmonary artery pressure; GI: gastrointestinal.
*"ever" means prior to the visit when BNP/TNT was measured.

Outcomes of interest

Patients enrolled in the study were followed for a mean of 3.0 ± 1.8 years. During this time, 101 (15.0%) patients died, 37 (6.4%) developed systolic dysfunction, 39 (5.8%) developed PAH, 43 (7.3%) developed PH, 18 (2.9%) developed arrhythmias, and 48 (12.3%) developed interstitial lung disease. The incidence rate of death was 43.7 per 1000 person-years, systolic dysfunction was 18.9 per 1000 person-years, pulmonary artery hypertension was 15.7 per 1000 person-years, PH was 22.2 per 1000 person-years, arrhythmia was 8.7 per 1000 person-years, and interstitial lung disease was 37.3 per 1000 person-years.

Relationship between patient characteristics and outcomes of interest

In univariate analysis, death was associated with age, sex, hypertension, BMI $> 30\,kg/m^2$, myocardial infarction, congestive heart failure, cerebrovascular event, dyspnea, FVC % predicted, DLCO % predicted, and SPAP (all p-values < 0.05) (Table 2). Systolic dysfunction was associated with age, hypertension, BMI $> 30\,kg/m^2$, congestive heart failure, modified Rodnan skin score, diffuse cutaneous SSc, dyspnea, DLCO %predicted, and systolic pulmonary arterial pressure (all p-values < 0.05). PAH was associated with dyspnea, FVC % predicted, DLCO % predicted, and systolic pulmonary arterial pressure (all p-values < 0.05). PH was associated with modified Rodnan skin score, scleroderma renal crisis, dyspnea, FVC % predicted, DLCO % predicted, systolic pulmonary arterial pressure, and digital ulcers (all p-values < 0.05). Arrhythmia was associated with age, BMI $> 30\,kg/m^2$, myocardial infarction, cerebrovascular event, disease duration from first non-Raynaud's symptoms, and gastrointestinal involvement assessed with the GI-14 questionnaire (all p-values < 0.05). Interstitial lung disease was associated with modified Rodnan skin score, FVC % predicted, and anti-centromere antibodies (all p-values < 0.05).

Relationship between NT-proBNP, hs-cTnT, and CRP and outcomes of interest

NT-proBNP, hs-cTnT, and CRP were analyzed as continuous variables. In univariate analysis, death was associated with elevated NT-proBNP, hs-cTnT, and CRP. Systolic dysfunction was associated with elevated hs-cTnT. PAH was associated with elevated NT-proBNP, hs-cTnT, and CRP. PH was associated with elevated NT-proBNP, hs-cTnT, and CRP. Arrhythmia was associated with elevated NT-proBNP and hs-cTnT. Finally, interstitial lung disease was associated with elevated NT-proBNP and hs-cTnT (all p-values were less than 0.05).

Multivariate analyses

Cox proportional hazard models were performed to investigate the association between NT-proBNP, hs-cTnT, and CRP and the outcomes of interest, after adjusting for covariates (Table 3). In separate models, death was associated with elevated NT-proBNP (model **b** hazard ratio (HR) for log2NT-proBNP 1.24, 95% confidence interval (CI) 1.09, 1.41), hs-cTNT (model **c** HR for log2hs-cTNT 1.28, 95% CI 1.13, 1.45), and CRP (model **d** HR 1.19 for log2CRP, 95% CI 1.05, 1.35). In other words, doubling the NT-proBNP, hs-cTNT, and CRP values are equivalent to a 24%, 28%, and 19% increase in the risk of death, respectively. The model with the best fit included all three variables (model **h** AIC 1077, C statistic by cross validation 0.779), although hs-cTnT, alone (model **c**) and in combination with CRP (model **g**), was associated with almost as good model fit.

NT-proBNP was associated with PH alone (HR for log2NT-proBNP 1.29, 95% CI 1.06, 1.58) and CRP (HR 1.32, 95% CI 0.94, 1.85) in combination with hs-TNT and CRP, both alone (models **e** and **f**) and together (model **h**). Thus, doubling the NT-proBNP value is associated with approximately 30% increase in the risk of PH. However, addition of hs-TNT and CRP did not improve prediction beyond NT-proBNP alone.

Although NT-proBNP was associated with PAH in models **e** and **h**, its addition as well as the addition of hs-cTNT and CRP did not add to the prediction of this outcome, beyond the clinical variables.

Systolic dysfunction and interstitial lung disease were not significantly associated with any of the three biomarkers either alone or in combination and their addition to the basic model (model **a**) did not add to the prediction. A multivariate model for arrhythmia could not be created as the number of events (18) was too low relative to the number of variables selected for the model.

Discussion

In this cohort study, we measured serum NT-proBNP, hs-cTnT, and CRP in 675 SSc patients and followed them for the development of adverse cardiopulmonary outcomes. In multivariate analyses, elevated levels of NT-proBNP, hs-cTnT, and CRP were associated with increased risk of death, while elevated levels of NT-proBNP and CRP were associated with increased risk of PH.

Several studies have shown that NT-proBNP, hs-cTnT, and CRP levels are increased in SSc patients compared to healthy controls even in the absence of overt cardiac or lung disease.[13,16,17] It was postulated that elevated levels of these biomarkers could reflect subclinical myocardial damage associated with SSc. However, despite interest in identifying new screening tools for SSc complications, the studies so far have not led to the regular use of these

Table 2. Patient characteristics by the outcomes of interest.

	Death			Systolic dysfunction			Arrhythmias		
	Yes (N = 101)	No (N = 574)	p-value	Yes (N = 37)	No (N = 539)	p-value	Yes (N = 18)	No (N = 609)	p-value
Age, years	61.4 (10.9)	57.6 (11.3)	0.002	61.4 (9.0)	57.3 (11.6)	0.037	63.9 (10.0)	57.7 (11.3)	0.021
Female	78 (77.2%)	519 (90.4%)	<0.001	32 (86.5%)	488 (90.5%)	0.391	16 (88.9%)	542 (89.0%)	0.988
White	89 (89.0%)	503 (90.8%)	0.573	36 (97.3%)	471 (90.6%)	0.278	17 (94.4%)	534 (90.5%)	0.878
Cardiovascular risk factors									
Smoking (ever)	58 (58.0%)	339 (59.6%)	0.767	26 (70.3%)	313 (58.7%)	0.167	13 (72.2%)	356 (59.0%)	0.261
Hypertension	51 (50.5%)	202 (35.3%)	0.004	21 (56.8%)	176 (32.7%)	0.003	9 (50.0%)	217 (35.7%)	0.213
Diabetes	12 (11.9%)	41 (7.2%)	0.109	4 (10.8%)	28 (5.2%)	0.292	2 (11.1%)	43 (7.1%)	0.855
BMI > 30 kg/m^2	24 (24.2%)	89 (15.8%)	0.041	14 (37.8%)	79 (15.0%)	<0.001	7 (38.9%)	98 (16.4%)	0.030
Comorbidities									
Myocardial infarction	13 (12.9%)	27 (4.8%)	0.002	4 (10.8%)	18 (3.4%)	0.067	7 (38.9%)	19 (3.2%)	<.001
Congestive heart failure	20 (19.8%)	51 (9.0%)	0.001	9 (24.3%)	28 (5.2%)	<.001	4 (22.2%)	44 (7.3%)	0.059
Peripheral vascular disease	4 (4.0%)	20 (3.5%)	0.824	3 (8.1%)	17 (3.2%)	0.266	2 (11.1%)	19 (3.2%)	0.237
Cerebrovascular accident	10 (9.9%)	24 (4.2%)	0.017	2 (5.4%)	19 (3.6%)	0.900	3 (16.7%)	24 (4.0%)	0.044
Disease duration, years									
From 1st NR symptom	13.4 (8.6)	13.7 (9.2)	0.860	11.3 (7.7)	13.4 (8.8)	0.149	18.7 (11.1)	13.1 (8.6)	0.018
From onset of RP	16.5 (11.0)	17.9 (12.2)	0.437	14.5 (9.5)	17.6 (12.0)	0.164	24.5 (19.1)	17.3 (11.6)	0.158
Modified Rodnan Skin Score	10.4 (11.4)	8.0 (8.0)	0.169	10.5 (10.2)	7.8 (8.2)	0.026	7.8 (9.2)	8.2 (8.5)	0.647
Diffuse cutaneous SSc	48 (47.5%)	253 (44.1%)	0.520	24 (64.9%)	225 (41.7%)	0.006	9 (50.0%)	271 (44.5%)	0.644
Scleroderma renal crisis	6 (5.9%)	21 (3.7%)	0.421	2 (5.4%)	18 (3.3%)	0.842	0	26 (4.3%)	0.768
Shortness of Breath	3.2 (2.9)	1.8 (2.4)	<0.001	2.9 (2.6)	1.7 (2.4)	0.001	2.5 (2.7)	1.9 (2.5)	0.180
FVC, %predicted	80.7 (18.1)	93.8 (18.5)	<0.001	88.4 (13.5)	93.5 (18.7)	0.051	91.9 (15.4)	92.3 (19.2)	0.747
DLCO, %predicted	52.6 (20.7)	71.6 (20.4)	<0.001	58.6 (16.9)	71.1 (21.3)	0.001	59.2 (15.0)	69.9 (21.6)	0.068
SPAP, mmHg	45.3 (21.4)	32.7 (13.3)	<0.001	41.0 (20.3)	32.7 (13.2)	0.004	38.2 (13.9)	34.0 (14.9)	0.235
Inflammatory myositis	3 (3.0%)	37 (6.5%)	0.168	3 (8.1%)	29 (5.4%)	0.492	2 (11.1%)	32 (5.3%)	0.586
Inflammatory arthritis	11 (11.1%)	97 (17.1%)	0.137	6 (16.2%)	77 (14.5%)	0.772	5 (29.4%)	94 (15.6%)	0.232
GI-14	3.4 (3.1)	2.9 (2.7)	0.294	3.0 (2.2)	2.9 (2.8)	0.295	4.5 (3.1)	2.9 (2.7)	0.027
Digital ulcers	45 (44.6%)	197 (34.6%)	0.054	15 (40.5%)	193 (36.1%)	0.585	8 (44.4%)	219 (36.2%)	0.474
Antibodies									
Anti-centromere	32 (34.4%)	214 (40.2%)	0.296	16 (44.4%)	195 (39.3%)	0.544	7 (38.9%)	219 (39.0%)	0.995
Anti-topoisomerase I	18 (19.4%)	79 (14.8%)	0.265	5 (13.9%)	80 (16.1%)	0.723	2 (11.1%)	89 (15.8%)	0.587
Anti-RNA polymerase III	16 (17.2%)	76 (14.3%)	0.459	8 (22.2%)	70 (14.1%)	0.184	2 (11.1%)	88 (15.7%)	0.600
Biomarkers, median [IQR]									
hs-cTnT	10.0 [5.0, 22.0]	5.0 [1.0, 9.0]	<0.001	7.0 [4.0, 17.0]	5.0 [1.0, 8.0]	0.005	7.5 [6.0, 25.0]	5.0 [3.0, 9.0]	0.019
BNP	227 [99,571]	114 [61, 219]	<0.001	164 [52, 431]	110 [62, 201]	0.218	295 [117, 663]	113 [61, 222]	0.003
CRP	5.2 [2.7, 11.0]	3.0 [1.0, 6.6]	<0.001	3.6 [2.4, 8.7]	3.0 [1.0, 6.8]	0.185	6.0 [3.6, 9.1]	3.0 [1.1, 7.3]	0.066
	Pulmonary hypertension			Pulmonary arterial hypertension			Interstitial lung disease		
	Yes (N = 43)	No (N = 543)	p-value	Yes (N = 39)	No (N = 636)	p-value	Yes (N = 48)	No (N = 341)	p-value
Age, years	59.9 (9.9)	57.1 (11.4)	0.118	60.1 (8.1)	58.0 (11.4)	0.138	56.8 (13.0)	56.5 (11.4)	0.704
Female	34 (79.1%)	482 (88.8%)	0.059	33 (84.6%)	564 (88.7%)	0.608	42 (87.5%)	316 (92.7%)	0.340
White	40 (95.2%)	468 (89.3%)	0.340	35 (97.2%)	557 (90.1%)	0.263	41 (89.1%)	302 (92.4%)	0.452
Cardiovascular risk factors									
Smoking (ever)	27 (62.8%)	320 (59.6%)	0.680	21 (55.3%)	375 (59.5%)	0.604	31 (64.6%)	196 (58.3%)	0.410
Hypertension	19 (44.2%)	189 (34.9%)	0.219	15 (38.5%)	238 (37.5%)	0.902	19 (39.6%)	120 (35.3%)	0.561
Diabetes	5 (11.6%)	40 (7.4%)	0.488	4 (10.5%)	49 (7.8%)	0.762	5 (10.4%)	16 (4.8%)	0.162
BMI > 30 kg/m^2	8 (19.1%)	86 (16.2%)	0.627	10 (25.6%)	103 (16.6%)	0.144	9 (19.2%)	47 (14.0%)	0.353
Comorbidities									
Myocardial infarction	2 (4.7%)	29 (5.4%)	0.836	4 (10.5%)	36 (5.7%)	0.387	4 (8.3%)	14 (4.2%)	0.261
Congestive heart failure	7 (16.3%)	43 (8.0%)	0.062	7 (18.4%)	64 (10.1%)	0.181	7 (14.6%)	24 (7.1%)	0.089
Peripheral vascular disease	3 (7.0%)	17 (3.2%)	0.375	1 (2.6%)	23 (3.7%)	1.000	4 (8.3%)	13 (3.9%)	0.248
Cerebrovascular accident	3 (7.0%)	27 (5.0%)	0.841	3 (7.9%)	31 (4.9%)	0.665	2 (4.2%)	13 (3.9%)	0.921
Disease duration, years									
From 1st NR symptom	12.0 (8.9)	13.4 (8.8)	0.172	13.7 (10.9)	13.7 (9.0)	0.561	12.4 (9.7)	13.5 (8.8)	0.323
From onset of RP	14.9 (11.8)	17.5 (11.8)	0.159	19.0 (13.5)	17.6 (11.9)	0.638	17.1 (15.3)	17.9 (11.7)	0.203
Modified Rodnan Skin Score	13.9 (12.7)	7.8 (7.9)	0.001	11.4 (11.9)	8.1 (8.3)	0.111	10.5 (10.5)	6.5 (7.2)	<0.001
Diffuse cutaneous SSc	25 (58.1%)	243 (44.8%)	0.090	20 (51.3%)	281 (44.2%)	0.387	21 (43.8%)	119 (34.9%)	0.232
Scleroderma renal crisis	5 (11.6%)	19 (3.5%)	0.029	1 (2.6%)	26 (4.1%))	0.960	2 (4.2%)	9 (2.6%)	0.633
Shortness of breath	2.6 (2.6)	1.6 (2.3)	0.003	4.2 (3.1)	1.8 (2.5)	<0.001	1.5 (2.1)	1.6 (2.3)	0.973
FVC, %predicted	83.2 (19.2)	94.5 (18.0)	<0.001	78.9 (19.2)	92.7 (18.6)	<0.001	90.3 (15.0)	98.5 (16.1)	<0.001
DLCO, %predicted	54.8 (16.1)	72.8 (20.3)	<0.001	46.3 (15.7)	70.5 (20.9)	<0.001	69.5 (18.0)	75.9 (20.5)	0.054
SPAP, mmHg	34.2 (7.1)	29.3 (6.5)	<0.001	57.2 (26.2)	32.9 (12.8)	<0.001	34.0 (10.9)	32.1 (13.9)	0.158
Inflammatory myositis	1 (2.3%)	32 (5.9%)	0.522	1 (2.6%)	39 (6.2%)	0.565	5 (10.4%)	16 (4.7%)	0.161

(Continued)

Table 2. (Continued)

	Pulmonary hypertension			Pulmonary arterial hypertension			Interstitial lung disease		
	Yes (N = 43)	No (N = 543)	p-value	Yes (N = 39)	No (N = 636)	p-value	Yes (N = 48)	No (N = 341)	p-value
Inflammatory arthritis	4 (9.5%)	92 (17.1%)	0.203	2 (5.1%)	106 (16.9%)	0.053	7 (14.6%)	50 (14.9%)	0.957
GI-14	2.3 (2.4)	2.9 (2.7)	0.243	3.7 (2.7)	2.9 (2.7)	0.065	2.9 (2.8)	3.3 (2.8)	0.399
Digital ulcers	23 (53.5%)	191 (35.4%)	0.018	14 (35.9%)	228 (36.1%)	0.982	18 (37.5%)	107 (31.7%)	0.418
Antibodies									
Anti-centromere	13 (33.3%)	198 (39.3%)	0.463	16 (48.5%)	231 (39.0%)	0.276	16 (37.2%)	171 (54.8%)	0.030
Anti-topoisomerase I	7 (18.0%)	79 (15.7%)	0.708	5 (15.2%)	92 (15.5%)	0.955	6 (14.0%)	29 (9.3%)	0.409
Anti-RNA polymerase III	10 (25.6%)	72 (14.3%)	0.056	4 (12.1%)	88 (14.8%)	0.860	6 (14.0%)	38 (12.2%)	0.741
Biomarkers, median [IQR]									
hs-cTnT	7.0 [5.0, 17.0]	5.0 [1.0, 9.0]	<0.001	7.0 [4.0, 13.0]	5.0 [3.0, 10.0]	0.037	6.0 [2.0, 12.5]	4.0 [1.0, 7.0]	0.029
BNP	164 [80, 515]	107 [60, 196]	0.001	214 [64, 460]	120 [62, 247]	0.015	158 [76, 318]	107 [60, 191]	0.043
CRP	6.0 [3.2, 13.8]	3.0 [1.0, 6.3]	<0.001	5.5 [3.0, 9.8]	3.0 [1.1, 7.2]	0.009	3.2 [1.2, 7.4]	2.8 [1.0, 5.3]	0.113

CRP: C-reactive protein; BMI: body mass index; FVC: forced vital capacity; DLCO: diffusion capacity of the lungs for carbon monoxide; SPAP: systolic pulmonary artery pressure; GI: gastrointestinal; IQR: interquartile range; hs-cTnT: high-sensitivity cardiac troponin T; BNP: b-type natriuretic peptide.

Table 3. Cox proportional hazard models to relate the association between the biomarkers and outcomes of interest (hazard ratio (95% CI)).

	Model a	Model b (+NT-proBNP)	Model c (+hs-cTNT)	Model d (+CRP)	Model e (+NT-proBNP and Ths-cNT)	Model f (+NT-proBNP and CRP)	Model g (+hs-cTNT and CRP)	Model h (+BNP, TNT, and CRP)
Outcome: death								
Age, years	1.03 (1.01, 1.05)	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)	1.03 (1.01, 1.05)	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
Female	0.39 (0.24, 0.64)	0.37 (0.23, 0.60)	0.41 (0.25, 0.68)	0.38 (0.23, 0.62)	0.40 (0.25, 0.66)	0.36 (0.22, 0.59)	0.40 (0.24, 0.66)	0.39 (0.24, 0.64)
DLCO, %predicted	0.96 (0.95, 0.97)	0.97 (0.96, 0.98)	0.97 (0.96, 0.98)	0.97 (0.95, 0.98)	0.97 (0.96, 0.98)	0.97 (0.96, 0.98)	0.97 (0.96, 0.98)	0.97 (0.96, 0.98)
GI-14	1.07 (1.00, 1.15)	1.07 (0.99, 1.14)	1.08 (1.00, 1.16)	1.06 (0.99, 1.15)	1.08 (1.00, 1.16)	1.06 (0.99, 1.14)	1.07 (0.99, 1.16)	1.07 (0.99, 1.05)
Log2(NT-proBNP)		1.24 (1.09, 1.41)			1.12 (0.96, 1.29)	1.20 (1.06, 1.36)		1.10 (0.95, 1.27)
Log2(hs-cTNT)			1.28 (1.13, 1.45)		1.21 (1.05, 1.41)		1.25 (1.10, 1.42)	1.19 (1.03, 1.38)
Log2(CRP)				1.19 (1.05, 1.35)		1.15 (1.02, 1.31)	1.14 (1.00, 1.29)	1.13 (1.00, 1.29)
AIC	1093.68	1084.44	1079.89	1086.86	1079.60	1080.68	1077.15	1077.34
C statistics	0.747	0.768	0.775	0.762	0.779	0.778	0.781	0.786
C statistics by cross validation	0.743	0.763	0.769	0.759	0.774	0.773	0.775	0.779
Outcome: systolic dysfunction								
Hypertension	2.34 (1.18, 4.65)	2.06 (1.02, 4.16)	1.90 (0.90, 4.03)	2.34 (1.18, 4.65)	1.83 (0.86, 3.89)	2.06 (1.02, 4.16)	1.90 (0.89, 4.02)	1.82 (0.85, 3.88)
BMI > 30 kg/m^2	2.73 (1.37, 5.46)	3.41 (1.60, 7.28)	3.17 (1.53, 6.58)	2.72 (1.35, 5.51)	3.58 (1.66, 7.75)	3.48 (1.59, 7.61)	3.24 (1.52, 6.89)	3.72 (1.67, 8.28)
Congestive heart failure	4.36 (1.94, 9.78)	3.93 (1.72, 8.98)	4.31 (1.92, 9.68)	4.37 (1.94, 9.82)	4.05 (1.78, 9.21)	3.90 (1.71, 8.92)	4.27 (1.90, 9.61)	4.00 (1.76, 9.10)
Diffuse cutaneous SSc	2.93 (1.47, 5.84)	2.85 (1.43, 5.68)	2.69 (1.34, 5.42)	2.94 (1.47, 5.86)	2.70 (1.34, 5.43)	2.84 (1.42, 5.65)	2.67 (1.32, 5.39)	2.66 (1.31, 5.38)
DLCO, %predicted	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
Log2(NT-proBNP)		1.19 (0.94, 1.50)			1.14 (0.88, 1.47)	1.19 (0.94, 1.52)		1.14 (0.88, 1.48)
Log2(hs-cTNT)			1.17 (0.93, 1.47)		1.12 (0.87, 1.44)		1.18 (0.93, 1.49)	1.12 (0.87, 1.45)
Log2(CRP)				1.01 (0.81, 1.25)		0.98 (0.78, 1.22)	0.97 (0.78, 1.22)	0.96 (0.77, 1.20)
AIC	367.13	367.11	367.31	369.09	368.35	369.03	369.22	370.20
C statistics	0.825	0.834	0.830	0.826	0.835	0.834	0.829	0.833
C statistics by cross validation	0.820	0.828	0.801	0.819	0.801	0.825	0.800	0.798
Outcome: pulmonary hypertension								
mRSS	1.06 (1.03, 1.08)	1.06 (1.03, 1.08)	1.05 (1.02, 1.08)	1.05 (1.02, 1.08)	1.06 (1.03, 1.09)	1.05 (1.02, 1.08)	1.05 (1.01, 1.08)	1.06 (1.02, 1.09)
DLCO, %predicted	0.96 (0.94, 0.98)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
SPAP, mm Hg	1.06 (1.01, 1.12)	1.06 (1.01, 1.12)	1.06 (1.00, 1.12)	1.06 (1.01, 1.12)	1.06 (1.01, 1.12)	1.06 (1.00, 1.12)	1.06 (1.00, 1.12)	1.06 (1.01, 1.12)
Log2(NT-proBNP)		1.29 (1.06, 1.58)			1.34 (1.06, 1.71)	1.28 (1.05, 1.57)		1.35 (1.07, 1.71)
Log2(hs-cTNT)			1.07 (0.87, 1.31)		0.93 (0.74, 1.18)		1.04 (0.85, 1.28)	0.91 (0.72, 1.14)
Log2(CRP)				1.16 (0.95, 1.41)		1.15 (0.95, 0.41)	1.15 (0.94, 1.41)	1.17 (0.96, 1.42)
AIC	460.10	455.97	461.60	459.28	457.54	455.38	461.06	456.59
C statistics	0.809	0.825	0.813	0.812	0.823	0.825	0.814	0.822
C statistics by cross validation	0.802	0.819	0.802	0.800	0.809	0.814	0.809	0.804
Outcome: pulmonary arterial hypertension								
mRSS	1.04 (1.01, 1.07)	1.04 (1.01, 1.07)	1.05 (1.01, 1.08)	1.04 (1.01, 1.07)	1.05 (1.02, 1.09)	1.04 (1.01, 1.07)	1.05 (1.01, 1.08)	1.05 (1.02, 1.09)
DLCO, %predicted	0.95 (0.93, 0.97)	0.95 (0.93, 0.98)	0.95 (0.93, 0.97)	0.95 (0.93, 0.98)	0.95 (0.93, 0.97)	0.95 (0.93, 0.98)	0.95 (0.93, 0.97)	0.95 (0.93, 0.97)

(Continued)

Table 3. (Continued)

	Model a	Model b (+NT-proBNP)	Model c (+hs-cTNT)	Model d (+CRP)	Model e (+NT-proBNP and Ths-cNT)	Model f (+NT-proBNP and CRP)	Model g (+hs-cTNT and CRP)	Model h (+BNP, TNT, and CRP)
SPAP, mmHg	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)	1.03 (1.02, 1.05)	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)	1.03 (1.02, 1.05)	1.03 (1.01, 1.05)
Log2(NT-proBNP)		1.03 (0.82, 1.29)			1.05 (1.02, 1.09)	1.03 (0.82, 1.30)		1.05 (1.02, 1.09)
Log2(hs-cTNT)			0.87 (0.70, 1.09)		0.95 (0.93, 0.97)		0.87 (0.70, 1.09)	0.95 (0.93, 0.97)
Log2(CRP)				0.99 (0.80, 1.23)		0.99 (0.80, 1.23)	1.01 (0.81, 1.26)	1.00 (0.81, 1.25)
AIC	408.17	409.86	408.30	409.91	409.02	411.61	410.05	410.81
C statistics	0.860	0.860	0.862	0.860	0.859	0.859	0.862	0.859
C statistics by cross validation	0.857	0.856	0.858	0.856	0.855	0.855	0.858	0.854
Outcome: interstitial lung disease								
mRSS	1.03 (1.01, 1.06)	1.03 (1.01, 1.06)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)
FVC, %predicted	0.97 (0.95, 0.99)	0.98 (0.96, 1.00)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
Log2(NT-proBNP)		1.14 (0.94, 1.39)			1.13 (0.90, 1.42)	1.13 (0.93, 1.38)		1.13 (0.90, 1.42)
Log2(hs-cTNT)			1.07 (0.89, 1.28)		1.01 (0.82, 1.24)		1.06 (0.88, 1.27)	1.00 (0.81, 1.24)
Log2(CRP)				1.04 (0.87, 1.24)		1.03 (0.86, 1.23)	1.03 (0.86, 1.23)	1.03 (0.86, 1.23)
AIC	514.89	515.25	516.41	516.59	517.24	517.10	518.21	519.09
C statistics	0.639	0.647	0.644	0.639	0.648	0.647	0.643	0.648
C statistics by cross validation	0.642	0.639	0.642	0.639	0.625	0.635	0.641	0.622

NT-proBNP: N-terminal pro b-type natriuretic peptide; hs-cTnT: high-sensitivity cardiac troponin T; CRP: C-reactive protein; FVC: forced vital capacity; DLCO: diffusion capacity of the lungs for carbon monoxide; SPAP: systolic pulmonary artery pressure; GI: gastrointestinal; AIC: Akaike information criterion; BMI: body mass index; mRSS: modified Rodnan skin score.

biomarkers in routine clinical practice. Our findings suggest that measurement of these biomarkers can have prognostic value for death and PH.

There could be several reasons why the biomarkers did not perform well in multivariate analyses for systolic dysfunction, PAH, or interstitial lung disease. It is possible that the sample size may not have been adequate, as of the 675 patients, only 37 (6.4%) developed systolic dysfunction, 39 (5.8%) developed PAH, and 48 (12.3%) developed interstitial lung disease. In addition, subjects with known cardiopulmonary disease were excluded from the models and those included (without cardiopulmonary disease) had on average fairly long disease duration. We may have missed an association by failing to have captured data on established cases or in subjects with early SSc. Unfortunately, there were too few subjects with early disease ($n=43$ with <3 years) to restrict the analysis to that subset. Future studies in large inception cohorts will be required to validate these findings.

Limitations of this study include the fact that NT-proBNP and hs-cTnT were only measured once. Although serial measurements of these biomarkers could be another strategy to identify pre-clinical cardiac and respiratory complications arising from SSc, we did not have data to address this question. The study was also limited by an observational design and cannot be used to establish causation.

The strengths of the study include an unselected, multicentre cohort and longitudinal follow-up. This is also the largest study in terms of sample size examining the predictive value of NT-proBNP and hs-cTnT in SSc patients. The study also benefited from the CSRG registry collecting a large number of SSc-related disease complications and test results, which allowed for a comprehensive multivariate analysis. The biomarkers used in this study are also widely available as part of routine laboratory work-up and can be easily incorporated into clinical practice.

Conclusion

We measured NT-proBNP, hs-cTnT, and CRP levels in a large, unselected, and multicentre cohort of SSc patients free of cardiopulmonary disease and then followed the patients for the development of cardiac and lung disease. Elevated NT-proBNP, hs-cTnT, and CRP were associated with the risk of death and elevated NT-proBNP and CRP were associated with the risk of PH. These findings can inform the development of evidence-based screening tools for cardiac and lung involvement in SSc.

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