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Original article

Cardiac troponin T and NT-proBNP as diagnostic and prognostic biomarkers of primary cardiac involvement and disease severity in systemic sclerosis: A prospective study

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ABSTRACT

Objectives: The aim of our study was to define the role of high-sensitive cardiac troponin T (hs-cTnT) and NT-proBNP in identifying Systemic Sclerosis (SSc) patients with cardiac involvement and at higher risk of cardiac death.

Methods: Plasma hs-cTnT and NT-proBNP concentrations were measured in 245 SSc-patients.

Results: hs-cTnT and NT-proBNP levels were higher in SSc-patients than in healthy controls. Hs-cTnT levels were higher than 0.014 ng/ml in 32.3% SSc-patients, while NT-proBNP was above 125 pg/ml in 31.8% of them, irrespective of classical cardiovascular risk factor and of pulmonary arterial hypertension. Elevated hs-cTnT and NT-proBNP were associated with diffuse skin involvement and directly correlated with the skin score. Patients with increased cardiac markers presented a lower left-ventricular ejection fraction (LVEF) and a higher rate of right bundle branch block (RBBB) on electrocardiogram (ECG) compared to patients with normal cardiac enzymes.

During the follow-up, 12 SSc-patients experience a disease-related death; 9 of these were directly related to cardiac involvement (sudden cardiac death or heart failure) and the majority of them occurred among patients with increase of at least one cardiac biomarker. Long-term survival was worse in patients with increase of both cardiac biomarkers.

Conclusions: Evaluation of hs-cTnT and NT-proBNP levels may provide a tool to screen non-invasively SSc-patients for heart involvement. A higher incidence of impaired systolic function, ECG abnormalities and a poor outcome in SSc-patients with elevated cardiac enzymes suggests that they may be valuable screening biomarkers to detect a cardiac damage at early stages and to improve risk stratification.

1. Introduction

Systemic Sclerosis (SSc) is a connective tissue disease characterized by diffuse vascular damage, aberrant activation of immune system and fibrosis of the skin and internal organs [1]. Firstly postulated by Hein in 1926 [2], then recognized by Weiss in 1943 [3], cardiac involvement is

Abbreviations: SSc, Systemic Sclerosis; cTnT, cardiac troponin T; hs, high sensitive; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; PAH, pulmonary

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common in SSc, even though often unrecognized. SSc heart involvement is heterogenous and can be classified into indirect effects caused by other organ involvement (PAH or renal crisis) [4–6] or a direct cardiac involvement going along with progressive inflammation and fibrosis, as recently reported [7,8]. Depending on the diagnostic technique used, clinical incidence of cardiac involvement ranges from 15% to 35% [4,9], while autoptic studies identified heart abnormalities in virtually all SSc-patients [3,10]. Despite being often clinically silent, cardiac involvement represents one of the leading causes of death in SSc-patients, accounting alone for about one third of total deaths [11]. Biomarkers of cardiac damage are desperately needed for an early diagnosis and a prompt therapeutic intervention. The role of the N-terminal of the pro-hormone brain natriuretic peptide (NT-proBNP) as cardiac biomarker in SSc has been described to identify either primary cardiac involvement or pulmonary arterial hypertension (PAH) [12,13], while the role of troponin is underestimated in this disease [14–19] and prognostic role of these cardiac biomarkers is far from be recognized [18,20].

Cardiac Troponin T (cTnT) is the preferred biomarker for the detection of myocardial cell injury and it has a main role in diagnosing acute coronary syndromes [21]. Clinical investigations revealed that elevation of cTnT levels might result not only from ischemic, but also from other forms of myocardial cell injury. In fact, there are reversible causes of troponin release including increased cell membrane permeability, as in sepsis and inflammation. In these conditions, the elevation of cTnT levels can be probably due to a “demand ischemia”, myocardial strain or direct myocardial damage, such as in myocarditis [22]. Furthermore, cTnT is known to be a marker of poor prognosis in other conditions such as cardiac failure, pulmonary embolism [23] and type 2-diabetes with stable ischemic heart disease [24].

The aim of our study was to define whether plasma concentrations of high sensitivity cTnT (hs-cTnT) and NT-proBNP in a population of well-characterized SSc-patients could really be diagnostic and prognostic biomarkers in a follow-up of three and a half years.

2. Materials and methods

2.1. Study population

Two hundred and forty-five consecutive SSc-patients admitted to our Rheumatology Department were enrolled in this single center cohort study.

All the patients fulfilled the new ACR/EULAR 2013 classification criteria for SSc [25] and were classified in limited or diffuse subset according to LeRoy classification [26]. The extension of cutaneous involvement was evaluated with modified Rodnan skin score[mRSS]. A comprehensive assessment of disease characteristics and organ involvement was performed and activity [27] and severity indices were calculated [28]. Any symptoms suggestive of cardiac involvement, such as chest pain, palpitations, dyspnea, and/or signs of heart failure (*i.e.*, ankle edema, raised jugular pulse, pulmonary rales) were recorded and dyspnea was categorized into four classes according to the New York Heart Association[NYHA] classification criteria [29]. SSc patients with overlap syndromes, a history of coronary artery disease or transient/permanent ischemic stroke were excluded from the study. Data were collected prospectively and the reached median follow-up time was 43 months (range: 14–77 months from the time of hs-cTnT and NT-proBNP assessment). Follow-up data, including causes of death (SSc related or unrelated), were available for all patients.

Of the 245 SSc patients enrolled in this study, patients older than 75 years and patients with PAH confirmed by RHC and/or renal failure were excluded to avoid interference of age and these clinical conditions with the plasma levels of hs-cTnT and NT-proBNP.

Furthermore, in order to compare hs-cTnT and NT-proBNP levels between SSc-patients and controls, 30 age and sex matched healthy controls were enrolled.

The study is in agreement with the recommendations of the Declaration of Helsinki and of the local Ethical Committee (Catholic University of the Sacred Heart of Rome – protocol number 3822/14). All patients and healthy controls gave informed consent to participate.

2.2. Clinical investigations

All SSc patients underwent standard 12-leads electrocardiogram (ECG), two-dimensional (2D) Doppler echocardiogram, cardiovascular risk profile evaluation, pulmonary function tests (PFTs), nailfold videocapillaroscopy and complete blood tests. Detailed methods are available in the Supplemental File.

2.3. Laboratory testing

All SSc patients and healthy control blood samples were collected in the morning after an overnight fast and a resting period of 20 min. After centrifugation 1500 $\times g$ for 20 min at room temperature, plasma was separated.

Hs-cTnT was measured using the quantitative electrochemiluminescence immunoassay (Roche Diagnostic, Mannheim, Germany), an essay very specific for troponin-T isoforms present in human cardiac muscles which utilizes two monoclonal antibodies specifically directed against human hs-cTnT with an analytic range of 0.003–10 ng/ml. A concentration of 0.014 ng/ml has been identified as the 99th percentile of a healthy reference population with a coefficient of variation or imprecision of < 10% [30].

The concentrations of NT-proBNP were measured by sandwich immunoassay on an Elecsys 2010 instrument (Roche Diagnostic, Basel-Switzerland). NT-proBNP level was considered elevated if higher than 125 pg/ml, according to the manufacturer recommendations [31]. No detectable cross-reactivity was observed with atrial natriuretic peptide, N-terminal atrial natriuretic peptide or BNP.

2.4. Statistical analysis

Data were analysed using SPSS 22.0 (SPSS, Chicago, IL-USA). Continuous variables are reported as mean ± standard deviation (SD) or median (range) according with the distribution of the data, while categorical variables are reported as number and percentage. A univariable analysis was performed to compare SSc patients and healthy controls and to identify variables associated with an increase of cardiac enzymes. Analysis of categorical variables was performed with the chi-square test or Fisher's exact when appropriate. Analysis of continuous variables was performed with the Mann-Whitney *U* test.

Spearman's rank correlation test was used to assess the relationship between quantitative variables.

Receiver Operating Characteristic (ROC) curves were used in order to analyze the accuracy of troponin and NT-proBNP level in predicting cardiac death. The Area Under Curve (AUC) was used to assess the accuracy and, if at least equal to 0.7, a cut-off maximizing the product between sensitivity and specificity was chosen [32], according with the clinical settings.

Univariate survival analysis for cardiac death was performed using the Kaplan Meier approach and with log-rank test to compare survival curves. Statistical significance was defined as a p-value < .05.

3. Results

3.1. Baseline clinical characteristics of the SSc population

Demographic, clinical and immunological characteristics of 195 SSc-patients are summarized in Table 1. Twenty-eight patients (14.4%) had a history of skeletal myositis but, at the time of cardiac enzymes detection, only 16 (8.2%) presented an increase of total creatine-kinase (CK). Sixty patients (30.8%) experienced palpitations, while dyspnoea

Table 1
Demographic, immunological, clinical characteristics and cardiac markers of 195 SSc patients and 30 healthy controls.

Characteristics	195[§] SSc patients	30 healthy controls
Age, years, [median (range)]	56.0 (19–75)	54 (37–73)
Females, n (%)	172 (88.2)	27 (90.0)
Disease duration, years, [median (range)]	7.0 (1–47)	NA
Diffuse skin disease, n (%)	82 (42.1)	NA
Modified Rodnan skin score, [median (range)]	6.0 (0–42)	NA
ANA positivity without specificity, n (%)	195 (100.0)	NA
Anti-topoisomerase I positivity, n (%)	96 (49.2)	NA
Anticentromere positivity, n (%)	71 (36.4)	NA
History of digital ulcers, n (%)	103 (52.8)	NA
Interstitial lung involvement, n (%)*	100 (51.3)	NA
FVC, %, [median (range)]	97.5 (31–150)	NA
DLCO, % [median (range)]	54.0 (10–119)	NA
Systolic PAP > 40 mmHg, n (%)**	17 (8.7)	NA
PASP value on echoacrdiography, mmHg [median (range)]	27.0 (12–80)	NA
History of myositis, n (%)	28 (14.4)	NA
LV-EF on echocardiography, (%) [median (range)]	62.0 (23–83)	NA
LVEF < 55%, n (%)	32 (16.4)	0 (0.0)
Patients with palpitations, n (%)	60 (30.8)	0 (0.0)
Patients with dyspnoea, n (%)	120 (61.5)	0 (0.0)
hs-cTnT values, ng/ml [median (range)]	0.011 (0.005–0.76)	0.005 (0.004–0.013) ***
hs-cTnT values > 0.014 ng/ml, n (%)	63 (32.3)	0 (0.0)
NT-proBNP values, (pg/ml) [median (range)]	85.0 (5–13,020)	54.0 (19.8–236.0) ***
NT-proBNP values > 125 pg/ml, n (%)	62 (31.8)	4 (13.3)
Cardiac symptoms n (%)	47 (75.8)	0 (0.0)
Classical cardiovascular risk factors		
Smoking, n (%)	27 (13.8)	0 (0.0)
Arterial Hypertension, n (%)	26 (13.3)	0 (0.0)
Diabetes mellitus, n (%)	11 (5.6)	0 (0.0)
Dyslipidemia, n (%)	40 (20.5)	0 (0.0)
BMI > 30 kg/m^2, n (%)	14 (7.2)	0 (0.0)

[§] From the initial cohort, patients older than 75 years and patients with precapillary pulmonary arterial hypertension confirmed by RHC and/or renal failure were excluded. n: number; FVC: forced vital capacity; DLCO: diffusing lung carbon monoxide; PASP: pulmonary artery systolic pressure.

* Interstitial lung disease defined as presence of any fibrotic involvement on high-resolution computed tomography (HRCT) and/or a restrictive lung disease on PFTs.

** PASP > 40 mmHg on echocardiography. LV-EF: left ventricular ejection fraction; hs-cTnT: high sensitive cardiac troponin T; NT-proBNP: N-terminal pro Brain Natriuretic Peptide. BMI: body mass index.

*** $p < .05$ between scleroderma patients and healthy controls.

was present in 120 of theme (61.5%) and was usually mild: 47 patients complained a NYHA class I dyspnea (24.1%), 59 patients (30.2%) were in NYHA class II, while 14 patients (7.2%) were in NYHA class III- IV. One hundred and nine SSc patients (54.8%) were free of any traditional cardiovascular risk factors.

The median follow-up time for the SSc patients since the evaluation of cardiac biomarkers was 43 months (range:14–77 months).

3.2. Plasma levels of hs-cTnT and NTproBNP in SSc patients compared with healthy controls

Hs-cTnT levels were higher in SSc patients than in healthy controls as well as NT-proBNP levels (Fig. 1, Table 1). Hs-cTnT levels were above the upper limit in 63 SSc patients (32.3%), while NT-proBNP was higher than 125 pg/ml in 62 patients (31.8%). Among SSc patients, 26 presented an isolated increase of hs-cTnT (13.3%), 25 an isolated elevation of NT-ProBNP (12.8%), while 37 of them (19.0%) an elevation of both cardiac biomarkers.

3.3. Hs-cTnT levels and SSc clinical characteristics

Among the 63 patients with hs-cTnT levels above the upper limit in the general population, 45 (71.4%) complained of cardiac symptoms, while 18 (28.6%) did not. Levels of hs-cTnT increase according with NYHA class ($p < .0001$). Median levels of CK-MB were 3.0 ng/ml and 36 patients (18.5%) presented raised CK-MB levels (defined as level higher than 4 ng/ml). Twenty-six (13.3%) patients presented an increase of both hs-cTnT and CK-MB.

Mean levels of hs-cTnT were higher in patients with diffuse skin disease compared to patients with limited disease[(median (range):0.011 (0.005–0.76) *vs* median (range): 0.013 (0.005–0.028)ng/ml, respectively, $p < .001$)], (Fig. 1) and there was a mild correlation between hs-cTnT levels and mRSS ($R = 0.35$; $p < .0001$, 95%CI: 0.15–0.4) (Supplemental figure). The increase of hs-cTnT levels was associated with history of skeletal myositis ($p < .001$), despite comparable levels of CK in patients with and without elevated hs-cTnT levels.

Patients with elevated hs-cTnT presented a more severe cardiac involvement with a lower LVEF and a higher pulmonary arterial systolic pressure (PASP) on echocardiography, even if patients with PAH on RHC were excluded from the analysis. Hs-cTnT levels directly correlate with LVEF ($R = -0.48$; $p < .001$, 95%CI:-0.15–0.52). Elevated hs-cTnT was also associated with a higher rate of RBBB on ECG, but not with a prolungation of QTc interval (Table 2) or with ST-T wave abnormalities.

The association between elevated hs-cTnT and more severe disease was confirmed by the direct correlations between hs-cTnT and disease severity index ($R = 0.3$; $p = .003$, 95%CI:0.19–0.47), disease activity index ($R = 0.3$; $p = .003$; 95%CI:0.13–0.45) and CRP ($R = 0.2$; $p = .02$, 95%CI:0.09–0.35), as well as by the inverse correlation with forced vital capacity (FVC) ($R = -0.2$; $p = .01$,95%CI: -0.15/−0.47) (Supplemental figure). Patients with increased hs-cTnT, moreover, presented a more impaired FVC and diffuse capacity for carbon monoxide (DLCO) and more frequently presented a restrictive lung disease compared to patients with normal hs-cTnT levels (Table 2). No differences in the distribution of age and classical cardiovascular risk factors emerged between patients with and without increase of hs-cTnT.

3.4. NT-proBNP levels and SSc clinical characteristics

Levels of NT-proBNP and hs-cTnT directly correlate each other ($R = 0.5$; $p = .001$,95%CI:0.2–0.7) (Supplemental figure) and NT-proBNP levels were higher in patients with high hs-cTnT compared to patients without hs-cTnT increase (Table 2).

Patients with raised NT-proBNP more frequently presented a diffuse skin disease compared to patients without NT-proBNP increase and mean levels of NT-proBNP were higher in patients with diffuse skin disease compared to patients with limited disease [median (range): (15.0–13,020) *vs* 75.0 (5–5449) pg/ml, respectively, $p < .001$] (Fig. 1).

Moreover, SSc patients with NT-proBNP higher than 125 pg/ml were more likely to be anti-topoisomerase positive, to have history of digital ulcers and avascular areas on nailfold-videocapillaroscopy (Table 3).

Similarly, patients with elevated NT-proBNP levels presented a more severe cardiac involvement with a lower LVEF and a higher PASP on echocardiography. NT-proBNP increase was also associated with a higher rate of RBBB on ECG, but not with prolongation of of QTc interval (Table 3) or other ECG abnormalities.

Parallel to the results on hs-cTnT, patients with elevated NT-proBNP, had a more impaired FVC and DLCO values and more frequently presented a restrictive lung disease (Table 3).

No differences in the distribution of classical cardiovascular risk

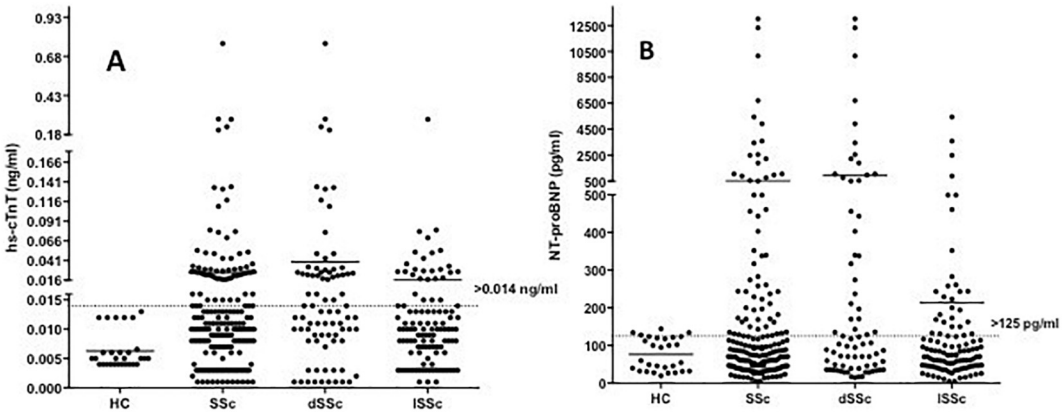

Fig. 1. Levels of high sensitive cTnT and NT-proBNP in patients with SSc and in healthy controls. Levels of high sensitive cTnT (A) and NT-proBNP (B) in scleroderma patients and in healthy controls. hs-cTnT: high sensitive cardiac troponin T. NT-proBNP: N-terminal of the prohormone brain natriuretic peptide. SSc: systemic sclerosis patients, dSSc: diffuse skin disease, lSSc: limited skin disease, HC: healthy controls. The dashed lines correspond to the cut off levels of cardiac biomarkers. The continuos lines represent the mean value for each group.

factors emerged between patients with and without increase of NT-proBNP, while a strict association between age and NT-proBNP values was observed, as expected.

3.5. Cardiac biomarkers and mortality

During the follow-up, 16 deaths occurred, and 12 were SSc-related; 9 of these were directly related to cardiac involvement (sudden cardiac death or heart failure) and 7 of them occurred among patients with increase of at least one cardiac biomarker (p = .005).

Patients who died initially presented with higher levels of hs-cTnT and of NT-proBNP and lower LVEF [hs-cTnT: median (range):0.07 (0.01–0.76); NT-proBNP: 2973 (61.0–13,020.0); LVEF: 40 (27–62)] than survivors [hs-cTnT: median (range):0.01 (0.001–0.28); NT-proBNP: 78 (5–5449); LVEF:62 (23–83); p = .001 for the comparisons].

Cumulative survival estimated by Kaplan-Meier curve was worse in patients with increased baseline levels of hs-cTnT (χ^2 = 10.2, p = .001) and with increased baseline levels of NT-proBNP (χ^2 = 11.1, p = .001), but the worst survival was associated with the combined increase of these two cardiac biomarkers (χ^2 = 13.5, p = .003), (Fig. 2 and

Table 2
Demographic, clinical, instrumental characteristics of patients with increased and normal high sensitive cTnT (hs-cTnT).

Characteristics	hs-cTnT ≥ 0.014 (63 pts)	Hs-hs-cTnT < 0.014 (132 pts)	P
Age, years [median (range)]	59.0 (19–75)	55.0 (23–75)	0.50
Male, n (%)	9 (14.3)	14 (10.6)	0.09
Disease duration, years [median (range)]	8.0 (1.0–47)	7.0 (1–42)	0.90
Anti-topoisomerase I positivity, n (%)	36 (57.1)	60 (46.2)	0.10
Anticentromere positivity, n (%)	16 (22.5)	55 (77.5)	0.02
Diffuse skin disease, n (%)	37 (58.7)	45 (34.1)	0.001
Skin score, [median (range)]	8.0 (0–42)	5.0 (0–42)	0.001
Digital ulcer history, n (%)	37 (58.7)	66 (50.0)	0.16
Presence of avascular areas on capillaroscopy, n (%)	47 (68.7)	53 (46.9)	0.20
Myositis history, n (%)	20 (31.7)	8 (6.1)	< 0.001
CK values above upper limits, n (%)	7 (11.1)	9 (6.8)	0.21
Right bundle branch block, n (%)	9 (15.8)	2 (1.5)	0.001
QTc interval > 440 ms, n (%)	9 (15.8)	8 (6.0)	0.06
QTc interval (ms), [median (range)]	414 (257–524)	408 (278–465)	0.10
NT-proBNP values (pg/ml), [median (range)]	171 (5–13,020)	65 (5–1054)	< 0.001
NT-proBNP values > 125 pg/ml, n (%)	37 (58.7)	25 (18.9)	< 0.001
CK-MB values, ng/ml [median (range)]	3.2 (0.8–60.4)	1.9 (0.1–13.0)	0.001
Interstitial lung involvement, n (%)*	35 (55.6)	65 (49.2)	0.05
Restrictive lung disease, n (%)**	19 (30.2)	21 (15.9)	0.007
FVC, %, [median (range)]	91 (35–128)	100 (31–150)	0.04
DLCO, % [median (range)]	46 (5–105)	56 (6–119)	0.05
LVEF, % [median (range)]	60 (23–83)	62 (54–78)	0.05
LVEF < 55%, n (%)	21 (33.3)	11 (8.3)	< 0.001
PASP on echocardiography, mmHg [median (range)]	30 (20–80)	25 (12–48)	0.01
SSc related cardiac death	7 (11.1)	2 (1.5)	0.005
Classical cardiovascular risk factors			
Smoking, n (%)	10 (15.9)	17 (12.9)	0.40
Arterial Hypertension, n (%)	8 (12.7)	18 (13.6)	0.53
Diabetes mellitus, n (%)	4 (6.3)	7 (5.3)	0.28
Dyslipidemia, n (%)	15 (23.8)	25 (18.9)	0.30
BMI > 30 kg/m^2, n (%)	3 (4.8)	11 (8.3)	0.30

hs-cTnT: high sensitivity cardiac troponin T, QTc: corrected QT interval on EKG, NT-proBNP: N-terminal pro Brain Natriuretic Peptide, CK-MB: creatin kinase MB isoform, FVC: forced vital capacity, DLCO: diffusing lung carbon monoxide, LV-EF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure.

* Patients with signs of fibrosis on high resolution computed tomography.

** Restrictive lung disease is defined when FVC ≤ 79%.

Table 3
Demographic, clinical and instrumental characteristics of patients with increased and normal NT-proBNP.

Characteristics	NT-proBNP ≥ 125 pg/ml (62 pts)	NT-proBNP < 125 pg/ml (133 pts)	P
Age, years [median (range)]	62.0 (19–75)	52.0 (23–75)	0.001
Male, n (%)	8 (12.9)	15 (11.3)	0.5
Disease duration, years [median (range)]	10.0 (1.0–47)	7.0 (1.0–42)	0.90
Anti-topoisomerase I positivity, n (%)	40 (64.5)	56 (42.1)	0.003
Anticentromere positivity, n (%)	20 (32.2)	51 (38.3)	0.3
Diffuse skin disease, n (%)	37 (59.7)	45 (33.8)	0.001
Skin score, [median (range)]	7.0 (0–42)	5.0 (0–26)	0.04
Digital ulcer history, n (%)	44 (70.9)	59 (44.3)	< 0.001
Presence of avascular areas on capillaroscopy, n (%)	44 (70.9)	56 (42.1)	< 0.001
Myositis history, n (%)	14 (22.6)	14 (10.5)	0.02
CK values above upper limits, n (%)	9 (14.5)	7 (5.2)	0.03
Right bundle branch block, n (%)	8 (12.9)	3 (1.5)	0.005
QTc interval > 440 ms, n (%)	9 (15.8)	8 (6.0)	0.06
QTc interval (ms), [median (range)]	416 (257–524)	407.5 (278–465)	0.10
hs-cTnT values (ng/ml), [median (range)]	0.017 (0.004–0.76)	0.009 (0.004–0.28)	0.001
hs-cTnT values > 0.014 ng/ml, n (%)	37 (58.7)	25 (18.9)	< 0.001
CK-MB values, ng/ml [median (range)]	2.4 (0.6–20.3)	2.1 (0.1–30.8)	0.007
Interstitial lung involvement, n (%)*	42 (67.7)	58 (43.6)	0.001
Restrictive lung disease, n (%)**	21 (33.9)	19 (14.3)	0.002
FVC, %, [median (range)]	90.5 (44–150)	97.5 (31–138)	0.02
DLCO, % [median (range)]	42.5 (5–113)	57.0 (6–119)	0.002
LVEF, % [median (range)]	60 (23–83)	62 (40–78)	0.002
LVEF < 55%, n (%)	20 (32.3)	12 (9.0)	< 0.001
PASP on echocardiography, mmHg [median (range)]	30 (18–80)	25 (12–50)	0.002
SSc related cardiac death	8 (12.9)	1 (0.8)	0.001
Classical cardiovascular risk factors			
Smoking, n (%)	8 (12.9)	19 (14.3)	0.5
Arterial Hypertension, n (%)	12 (19.3)	14 (10.5)	0.07
Diabetes mellitus, n (%)	3 (4.8)	8 (7.5)	0.5
Dyslipidemia, n (%)	15 (24.2)	25 (18.7)	0.2
BMI > 30 kg/m^2, n (%)	5 (8.0)	9 (6.8)	0.5

hs-cTnT: high sensitivity cardiac troponin T, QTc: corrected QT interval on EKG, NT-proBNP: N-terminal pro Brain Natriuretic Peptide, CK-MB: creatin kinase MB isoform, FVC: forced vital capacity, DLCO: diffusing lung carbon monoxide, LV-EF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure.

* Patients with signs of fibrosis on high resolution computed tomography.

** Restrictive lung disease is defined when FVC ≤ 79%.

Supplemental Table 2).

To study the role of hs-cTnT in predicting mortality, we performed a ROC curve analysis in order to determine the best hs-cTnT threshold capable of identifying patients who died for primary cardiac involvement. On ROC curve, hs-cTnt > 0.045 ng/ml showed 66.7% of sensitivity and 93% of specificity to predict SSc cardiac death [AUROC(95%CI): = 0.83 (0.68–0.98)](Fig. 3). Nineteen patients (9.7%) presented levels of hs-cTnT > 0.045 ng/ml.

Parallel, to assess the role of NT-proBNP in predicting bad outcome, we performed a ROC curve analysis in order to determine the best NT-proBNP threshold capable of identifying patients who died for primary cardiac involvement. On ROC curve, NT-proBNP > 649.5 pg/ml showed 77.8% of sensitivity and 94.6% of specificity to predict SSc cardiac death [AUROC (95%CI): = 0.89 (0.77–0.99)](Fig. 3). Seventeen patients (8.7%) presented NT-proBNP levels higher than 649.5 pg/ml.

Finally, given the clinical relevance of identifying SSc patients with

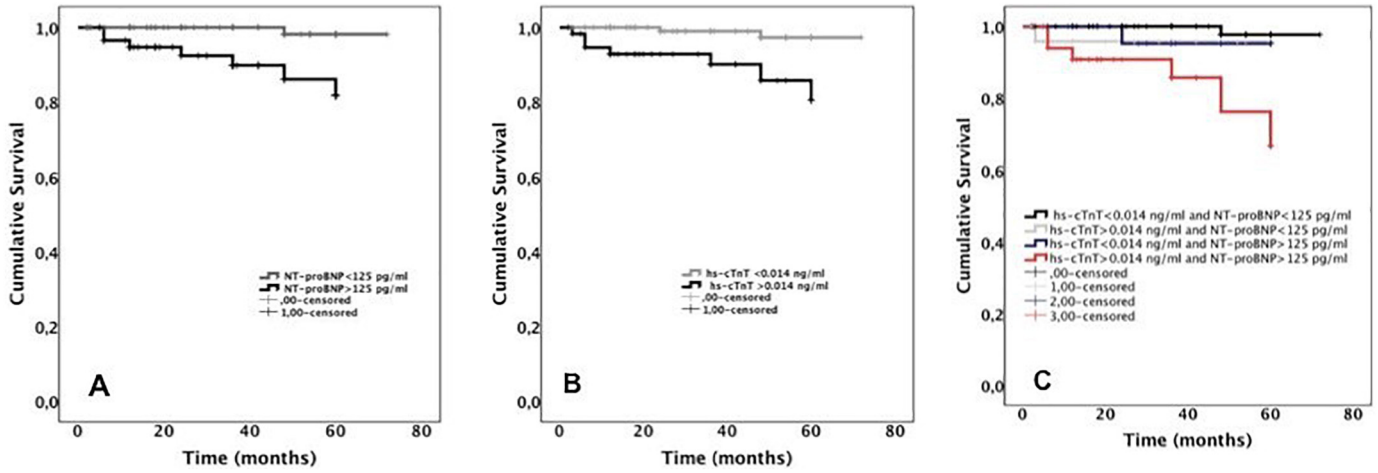

Fig. 2. Survival curves in patients with and without increased levels of cardiac biomarkers. Kaplan-Meier curves estimate cumulative survival between patients with or without increased of cardiac biomarkers. A: Kaplan Meier curve between patients with and without increased of hs-cTnT, B: Kaplan Meier curve between patients with and without increased of NT-proBNP, C: Kaplan Meier curve between patients with and without increased of NT-proBNP and/or hs-cTnT.

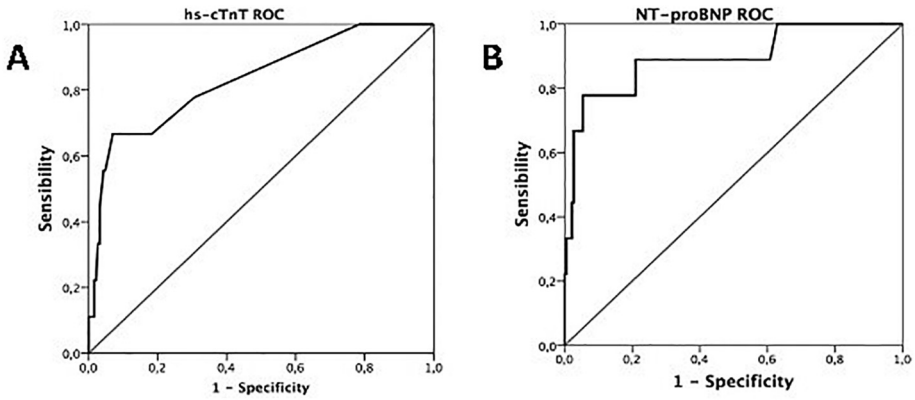

Fig. 3. ROC analysis of troponin and NT-proBNP level to predict cardiac death. Receiver Operating Characteristic (ROC) curves were used in order to analyze the accuracy of troponin and BNP level in predicting cardiac death maximizing the product between sensitivity and specificity. A: ROC curve for hs-cTnT; [AUC = 0.833 (0.684–0.981), p = .001] B:. ROC curve for Nt-proBNP [AUC = 0.893 (0.767–1.000), p < .001]. ROC = receiver operating curve. AUC = area under ROC.

suspected cardiac involvement that need further clinical and instrumental evaluation, we built a ROC curve analysis with high sensitivity either for hs-cTnT and NT-proBNP. On ROC curve, hs-cTnT > 0.014 ng/ml showed 77.8% of sensitivity and 69.4% of specificity to predict SSc cardiac death, and NT-proBNP > 175.5 pg/ml showed 88.9% of sensitivity and 79.5% of specificity to predict SSc cardiac deaths. This latest value for hs-cTnT correspond to the cut-off routinely used in clinical practice, while for NT-proBNP the cut-off value is very close to the cut-off proposed for general population. The conventional value of NT-proBNP of 125 pg/ml presented the high sensitivity but it slightly loose specificity (70.0%) (Supplemental Table).

4. Discussion

The majority of patients with SSc is thought to have subclinical primary cardiac involvement, even at early stages, but the occult nature of signs and symptoms and the lack of biomarkers and of a specific diagnostic algorithm make it misrecognized. Undetected early cardiac involvement is likely to progress to myocardial fibrosis and has to be considered as a harbinger of poor prognosis. In this scenario, precocious markers of cardiac damage are eagerly needed [4–7,11,33–36].

In our study, the levels of both hs-cTnT and NT-proBNP were higher in SSc population than in healthy controls, as previously reported [17]. > 30% of SSc-patients had an hs-cTnT concentration at baseline that was above the upper reference limit used to define myocardial injury, as well as and higher NT-proBNP concentrations, despite a relevant percentage of these patients did not complain of any symptoms.

Previous cross-sectional studies in limited number of patients had failed to identify elevated troponin levels in SSc [14,15]; recently though, the role of cTnT has been investigated in SSc patients with primary cardiac involvement and underlining myocardial inflammation [7,8,16–19,34–37]. Few studies also reported the usefulness of cardiac biomarkers in PAH [13,37]. In the present study, increased hs-cTnT levels were associated with an impaired ventricular systolic function, as supported by its inverse correlation with LVEF on echocardiography, as well as by its direct correlation with NT-proBNP serum levels. Furthermore, SSc patients with an increase of hs-cTnT more frequently presented RBBB on ECG, a recently recognized independent redictor of mortality in SSc [36]. Taken together, these data indirectly supports the usefulness of hs-cTnT as severity and prognostic biomarker. This latest hypothesis is further strengthened by survival data: during follow-up, the elevation of hs-cTnT was associated with increased risk of cardiac death in SSc patients, as previously reported for other conditions [21,23,24,38–41].

Our data lead us to conclude that hs-cTnT may be consider a marker of overall cardiac damage, irrespective of the presence of PAH, and a marker of disease severity that can identify a subgroup of patients with bad cardiac outcome.

It is generally accepted that cTnT is a marker of myocardial injury and it can increase not only in acute coronary syndromes, but also in several other conditions. Elevation of cTnT is a multifactorial event that can be related to an increased myocardial cell membrane permeability to cytoplasmic troponin pool like in sepsis, to a direct myocardial damage related to ischemia or to inflammation that determines the continuing breakdown of the myofibrillary bound complex after myocardial injury [23,42]. As in patients with heart failure, cTnT levels can be elevated also after clinical stabilization, indicating that cTnT is a biomarker of subclinical myocyte injury [38].

Although to our knowledge this is the largest study examining the incidence and the prognostic significance of hs-cTnT levels in SSc-patients without PAH, it is not possible to establish a pathogenic mechanism of cardiac damage in these patients. The pathogenesis of SSc-related heart disease is still controversial and poorly understood [5,6], mostly because our knowledge derived from post-mortem observations. It is possible that a “demand ischemia”, related to the presence of reversible vasospasm of small coronary vessels with structural organic abnormalities, induces myocardial injury with subsequent release of cTnT [5,6,36–40].

Moreover, the elevated levels of hs-cTnT may be due to the increased myocytes cell membrane permeability caused by cardiac inflammation with its cellular infiltration and cytokine release [5,42–45]. In that view, hs-cTnT elevation in SSc could be considered a marker of myocyte damage, which however can have a large range of severity from a transient leakage of the cytosolic component and the loss of sarcolemma integrity during reversible ischemia to its continuous release when ischemic or inflammatory injury is persistent and irreversible. The long-term consequences of persistently elevated cardiac enzymes in SSc remain unknown but may include conduction delay and life-threatening ventricular dysfunction [6,18,46–50].

Even though the pathogenic mechanisms that may determine the myocyte damage is unclear, hs-cTnT level measurement is a simple, repeatable and widely available test with a potential for improving early diagnosis of cardiac involvement in SSc. This clinical need leads us to suggest hs-cTnT as a useful screening tool to detect subclinical cardiac involvement and guide further investigations.

Natriuretic peptides have emerged as important candidates as diagnostic tools in cardiovascular disease. NT-proBNP plays a key role in the complex multi-organ and cellular adaptation in heart failure, regardless the initial injury [51,52]. Recent studies have demonstrated that NT-proBNP may be a sensitive and specific diagnostic [17,20,51–55] and prognostic marker in SSc patients with established PAH [13] and it may be useful also for the identification of primary heart dysfunction [12].

The association between increased NT-proBNP levels and diffuse cutaneous SSc in our study is consistent with the increased prevalence of cardiac manifestations reported in this subgroup of patients. As for troponin, the detection of increased NT-proBNP levels in the subgroup of SSc patients with more aggressive disease and at higher risk of increased mortality suggests its diagnostic and prognostic role as biomarker of cardiac involvement.

Main molecular mechanisms involved in synthesis and release of natriuretic peptides are not fully understood. Increased troponin levels may reflect the endothelial dysfunction and damage secondary to vasospasm or organic lesions of small arteries and coronary microcirculation, which is followed by the release of NT-proBNP in response to hemodynamic wall stress secondary to myocyte injury [13,42,53,56].

Survival data of our study suggest that raised hs-cTnT and NT-proBNP serum levels could be associated with an overall increased risk of death in SSc patients; interestingly though, SSc patients with elevation of both cardiac biomarkers seem to be those with the worst prognosis. These findings were independent of the possible confounding variables of traditional cardiovascular risk factors, renal function and presence of PAH. Even though the lack of data on multivariate analysis limits the possibility to drawn firm conclusions, hs-cTnT and NT-proBNP seem to be possible prognostic biomarkers in scleroderma and their prognostic role deserves further investigation. The use of a non-invasive blood test like hs-cTnT and NT-proBNP, indeed, may have important clinical implications in the early identification of SSc-patients who may have already developed or are at high-risk to develop disease-related cardiac complications and in the decision to perform further investigations for a prompt therapeutic intervention. It is therefore reasonable to measure hs-cTnT and NT-proBNP levels in every SSc patient, even in the asymptomatic ones. Thus, cardiac biomarkers evaluations could represent the initial step of an algorithm to identify SSc patients with cardiac involvement.

Our study should be interpreted with its limitations. We did not perform a systematic cardiac functional evaluation integrating measurements to assess right and left contractility and or diastolic dysfunction. Furthermore, this is an observational study and any link that emerges from this type of study should be taken very cautiously, either for the increase of hs-cTnT as well as for NT-proBNP.

5. Conclusions

Subclinical myocardial involvement in SSc is probably more relevant than previously appreciated, as revealed by the frequent detection of high hs-cTnT and NT-proBNP levels in SSc patients, especially in those with a more severe disease. Worse clinical status and higher incidence of both impaired systolic function and ECG abnormalities in patients with high cardiac biomarkers, suggest hs-cTnT and NT-proBNP as useful “biomarkers of cardiac damage” in SSc and predictors of poor long-term outcome. At present, it is reasonable to adopt a screening program with measurement of hs-cTnT and NT-proBNP in all SSc patients in order to identify at the earliest stages those with a heart disease and poor prognosis, thus allowing an early treatment and possibly reducing late deaths due to cardiac complications.

Declaration of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.10.013.

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