

## The renal resistive index, a new biomarker for the follow up of vascular modifications in Systemic Sclerosis

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A short running head: scleroderma and RRI

**Abstract**

**Objective:** The aim of the present retrospective observational study was to evaluate in SSc patients the change of renal resistive index (RRI) over the time ( $\Delta$ RRI) and under treatment as well as to correlate these changes with disease complications.

**Methods:** 230 patients [29 male, median age 57 (48-67) years] were enrolled. At baseline and follow-up [3.43 (2.81-4.45) years] we collected following data: disease variables, nailfold videocapilloscopy (NVC) pattern, FVC (Forced vital capacity), carbon oxide diffusing capacity (DLCO), systolic pulmonary arterial pressure (sPAP), presence of interstitial lung disease, RRI, evaluation of glomerular filtration rate (eGFR), new onset of pulmonary arterial hypertension (PAH).

**Results:** RRI value is high in SSc patients with digital ulcers and ACA antibodies, active and late NVC patterns, lcSSc. A significant correlation was observed between  $\Delta$ RRI and  $\Delta$ sPAP ( $r=0.17$ ,  $p=0.02$ ), with statistically higher  $\Delta$ RRI ( $0.08 \pm 0.02$  versus  $0.03 \pm 0.05$ ,  $p=0.04$ ) in patients complicated by PAH onset. No other new onset complication was associated with  $\Delta$ RRI. The ROC curve analysis confirmed the predictive role of  $\Delta$ RRI in development of new PAH (AUC 0.84; 95% CI 0.75-0.93,  $p=0.02$ ). In SSc patients never exposed to sildenafil,  $\Delta$ RRI was higher ( $0.04 \pm 0.05$ ) compared to both patients exposed to sildenafil during the study period ( $0.01 \pm 0.05$ ,  $p=0.03$ ) or in those exposed at the time of baseline evaluation ( $0.00 \pm 0.05$ ,  $p=0.01$ ).

**Conclusion:** RRI and its variation in time are a reliable marker of SSc related vasculopathy, both in renal and extra-renal compartments.

## Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by a complex pathogenesis (1). The disease affects the vascular system widely in the body, in particular the microcirculation of the fingers, lung, heart and kidney. In SSc, the kidney is frequently involved and renal manifestations range from reduction of glomerular filtrate rate (GFR), abnormal urinalysis, reduced renal functional reserve, antiphospholipid-associated nephropathy, myeloperoxidase-antineutrophil cytoplasmic antibody associated glomerulonephritis and vasculitis and a peculiar acute condition as scleroderma renal crisis (SRC). Among renal manifestations, scleroderma-associated vasculopathy is characterized by abnormal renal vascular resistance indices and endothelial markers (2). In SSc, the microcirculation of the kidney may be investigated with renal Doppler ultrasonography (RDU) (3) and the renal resistive index (RRI), which is a widely non-invasive tool used in physiological and pathological conditions (4). This technique allows a spectrum analysis of the arcuate arteries in the region of the corticomedullary junction and the interlobar arteries along the border of medullary pyramids. The increase of renal vascular resistances in renal artery stenosis (RAS), considering RRI as functional corresponding of structurally altered vasculature, has been previously described (5). In fact, RRI can detect modifications of the vascular distensibility, compliance and resistance due to pathologic mechanisms. In SSc, RRI is significantly increased and correlates with fibrotic and vascular features, that are mainly at the basis of the development of SRC (6), digital ulcers (DUs) (7) and capillaroscopic modifications (8). Since glomeruli account for 8% of the renal parenchymal thickness and the highest percentage is occupied by vascular and tubulo-interstitial components, RRI tends to be more sensitive to vascular lesions than glomerulonephritis (9). In fact, in several studies RRI correlates with pathologic lesions such as arteriolosclerosis, glomerulosclerosis, tubulo-interstitial damage and vascular lesions(10-11). A SSc autopsy case-control study, found a significant number of abnormalities in the small arteries of SSc patients than healthy controls. Although the most renal vascular structural changes were found in patients with SRC, the authors

showed a significant increase in absolute intimal area and luminal occlusion in all vessels in SSc patients with or without SRC (12). RRI increased with age and in several condition (e.g. arterial hypertension and renal arterial stenosis), a value of RRI greater than 0.70 is considered pathological. In our previous study, we showed that a cut off of RRI greater than 0.68 is predictive of mortality (sensitivity 88.5%, specificity 50.9%). We can assume that RRI values  $\geq 0.68$  and  $\leq 0.70$  are moderately high and values  $> 0.70$  are strongly increased (7, 13).

In SSc patients with normal renal function and blood pressure, a subclinical renal vascular disease has been demonstrated (14). In fact, vascular abnormalities were detected in renal pathological specimens obtained from non SRC patients with a three years follow-up (15). This evidence clearly demonstrates that SSc renal involvement is often subclinical and is tightly related to vascular injury and consequent chronic hypoxia which usually has a better prognosis than SRC (16).

The aim of the present retrospective observational study was to evaluate in SSc patients the change of RRI over the time ( $\Delta$ RRI) and under treatment as well as to correlate these changes with disease complications.

## **Materials and methods**

### *Study population*

Patients affected by SSc, classified according to American College of Rheumatology/European League Against Rheumatism criteria for SSc (17), and undergoing two RRI determinations on RDU since SSc diagnosis were retrospectively enrolled in the study. Patients were categorized as Very early systemic sclerosis patients (VEDOSS), if they were fulfilling the ACR/EULAR 2013 criteria only with the presence of the diagnostic VEDOSS criteria (18), otherwise as established SSc. Subsets of SSc cutaneous involvement were defined according to LeRoy et al (19).

Patients with renal failure, SRC, RAS, glomerulonephritis, pulmonary disease unrelated to SSc and cardiac failure were excluded, as well as pregnant or breastfeeding women. The study complies

with the Declaration of Helsinki. The local ethical committee approved the research protocol (CEAVC 12350\_oss) and informed consent was obtained from all patients.

#### *Data collection*

At baseline and follow-up, clinical, instrumental and functional data were collected. The following parameters were obtained: age, disease duration (from first non-Raynaud's symptom), presence of telangiectasias, presence of dyspnoea, presence/history of DUs (20), modified Rodnan skin score (mRSS) (21), gastrointestinal and joint involvement as clinical features; nailfold videocapilloscopy (NVC) pattern (2), FVC (Forced vital capacity), carbon oxide diffusing capacity (DLCO) corrected for hemoglobin concentration (23), systolic pulmonary arterial pressure (sPAP) on transthoracic echocardiography (24), presence of interstitial lung disease (ILD) at high resolution computerized tomography (HRCT), history of pulmonary arterial hypertension (according to international guidelines) (25), RRI on RDU (6) as instrumental data, evaluation of glomerular filtration rate (eGFR) (26) and autoantibody positivity as laboratory data. During follow-up, new onset of telangiectasias, DU, PAH, ILD, dyspnoea and SRC were also recorded.

#### *Statistical analysis*

All results are expressed as mean  $\pm$  SD or median and IQR, as appropriate. SPSS version 25.0 software was used for the statistical analysis. The coefficient of kurtosis was used to evaluate normal distribution of data. A multivariate analysis was applied for the estimation of the relationship of RRI with the clinical features. A receiver operating characteristic (ROC) curve analysis was performed to analyze the prognostic accuracy of RRI toward development of outcomes in the follow-up. All time-to-event end points were estimated with the Kaplan–Meier method and analyzed with the log-rank test. Hazard ratios with 95% confidence intervals were calculated with the use of Cox regression models. Group comparisons were made by Student's unpaired 2-tailed t-test or Mann-Whitney test, as appropriate. Pearson product-moment correlation coefficient or

Spearman's rank correlation coefficient, as appropriate, were used to test for an association between numerical variables. The chi-square test or Fisher's exact test, as appropriate, were used to compare categorical variables. P-values <0,05 were considered significant.

## Results

Two hundred and thirty patients [(29 male, median age 57 (48-67) years] were enrolled in the protocol: 30 satisfied the ACR/EULAR 2013 criteria with VEDOSS features only, while 200 presented with establish SSc; 65 (28.3%) had diffuse (dcSSc), 132 (57.4%) limited SSc (lcSSc) and 33 (14.3%) a sine scleroderma subset. In Table 1, the baseline clinical features of SSc patients are shown. The median value of eGFR was 97.5 ml/min (80.2-118.7) and median value of RRI was  $0.68 \pm 0.07$ . In ACA positive SSc patients, the RRI values were higher than in patients characterized by the presence of other autoantibodies ( $0.70 \pm 0.06$  vs  $0.68 \pm 0.07$ ;  $p=0.010$ ). In SSc patients with DUs, the mean RRI value was significantly higher when compared to SSc patients without DU ( $0.70 \pm 0.06$  vs  $0.68 \pm 0.07$ ;  $p=0.011$ ). The VEDOSS patients did not show any difference in RRI values when compared to those affected by an overt disease ( $0.68 \pm 0.06$  vs  $0.69 \pm 0.07$ ;  $p=0.743$ ). Meanwhile, the RRI value was significantly ( $p=0.010$ ) higher in lcSSc ( $0.70 \pm 0.07$ ) than sine scleroderma ( $0.67 \pm 0.06$ ) and dcSSc ( $0.68 \pm 0.07$ ). No significant difference of RRI value was observed between sine scleroderma and dcSSc. Patients with an active and late NVC patterns showed RRI values significantly higher than SSc patient with non-specific and early patterns ( $0.67 \pm 0.07$  vs  $0.69 \pm 0.06$ ,  $p=0.031$ ).

In Table 2 the changes ( $\Delta$ ) of SSc features during a median follow-up of 3.4 (2.8-4.4) years are shown. No significant correlation was observed between  $\Delta$ RRI and  $\Delta$ mRSS ( $r=0.112$ ,  $p=0.119$ ) or  $\Delta$ FVC ( $r=0.026$ ,  $p=0.712$ ) or  $\Delta$ DLCO ( $r=-0.091$ ,  $p=0.189$ ) or  $\Delta$ eGFR ( $r=-0.106$ ,  $p=0.133$ ). Conversely, a significant correlation was observed between  $\Delta$ RRI and  $\Delta$ sPAP ( $r=0.173$ ,  $p=0.023$ ), with statistically higher  $\Delta$ RRI ( $0.08 \pm 0.02$  versus  $0.03 \pm 0.05$ ,  $p=0.038$ ) in patients complicated by PAH onset (Table 3). Five (2.2%) SSc patients had new onset of SRC. No significant differences of

$\Delta$ RRI was observed between SSc patients with or without new onset of SRC ( $0.04 \pm 0.06$  vs  $0.03 \pm 0.05$ ,  $p=0.535$ ). No other new onset complication was associated with  $\Delta$ RRI (Table 3).

At univariate regression analysis,  $\Delta$ RRI [HR 7.127 (0.996-9.101),  $p=0.05$ ],  $\Delta$ sPAP [HR 1.082 (1.038-1.128),  $p<0.001$ ] and disease duration [HR 1.077 (1.006-1.154),  $p=0.034$ ] were predictive of new onset of PAH, although only  $\Delta$ sPAP was independently associated with new PAH onset [HR 1.076 (1.022-1.134),  $p=0.006$ ] at multivariate analysis (Supplement table 1). The ROC curve analysis confirmed the predictive role of  $\Delta$ RRI in development of new PAH (AUC 0.841; 95% CI 0.753-0.930,  $p=0.019$  – Figure 1). Interestingly, a significant difference of  $\Delta$ eGFR was also observed between SSc with PAH and SSc patients without PAH ( $-22.4 \pm 25.5$  vs  $-8.4 \pm 17.9$  ml/min,  $p=0.026$ ).

In Table 4, the pharmacological treatments are reported at baseline and follow-up, while the  $\Delta$ RRI in different classes of drug therapies are shown in table 5. In SSc patients never exposed to sildenafil,  $\Delta$ RRI was higher ( $0.03 \pm 0.05$ ) compared to both patients exposed to sildenafil during the study period ( $0.01 \pm 0.05$ ,  $p=0.028$ ) or in those exposed at the time of baseline evaluation ( $0.00 \pm 0.05$ ,  $p=0.009$ ). No significant  $\Delta$ RRI differences were observed when compared to SSc patients newly treated during follow-up ( $0.02 \pm 0.05$ ,  $p=0.582$ ). Conversely,  $\Delta$ RRI was lower in patients not exposed to CCB during the study period ( $0.02 \pm 0.04$ ) compared to those treated with CCB during the study ( $0.03 \pm 0.05$ ,  $p=0.027$ ) or exposed to CCBs at baseline ( $0.03 \pm 0.06$ ,  $p=0.033$ ). No significant differences of  $\Delta$ RRI were observed between SSc patients newly treated during follow-up and SSc patients treated during the study period ( $0.03 \pm 0.04$  vs  $0.03 \pm 0.05$ ,  $p=0.477$ ). In SSc patients treated with Iloprost at some point during the study period,  $\Delta$ RRI was higher than in untreated patients ( $0.03 \pm 0.05$  vs  $0.02 \pm 0.05$ ,  $p=0.033$ ). No significant differences of  $\Delta$ RRI were observed in SSc patients treated with iloprost at baseline or newly treated during follow-up, same as for the other vasodilative and vasoactive drugs listed in Table 5.

## Discussion



Our data clearly show that the  $\Delta$ RRI is changing progressively during the 3.4 years of follow-up. Moreover, it correlated with  $\Delta$ sPAP and was significantly higher in patients with new onset of PAH. In SSc, PAH is a severe vascular complication most commonly occurring in limited cutaneous ACA positive patients (27). In our population, ACA positive/limited cutaneous patients showed a higher RRI than ACA negative and diffuse cutaneous subset or sine scleroderma patients. Similarly, patients with DUs showed a higher RRI than patients without DUs, confirming RRI as a reliable marker of new DUs occurrence (6).

Although several manifestations of renal involvement are described, SRC remains one of the most feared complications of scleroderma. It was the most severe complication in scleroderma and was the most frequent cause of death in these patients. It is characterized by episodic renal vasospasm and proliferative obliterative vasculopathy with acute onset of moderate-to-severe hypertension and oliguric renal failure (2). Asymptomatic increased renal stiffness are reported in several studies and it showed an inverse correlation with glomerular filtration rate. In addition, increase of RRI may predict the occurrence of new digital ulcers and it increased with capillaroscopic damage (6-8).

These associations reflect the link between RRI and vascular involvement in different organs during the disease course. In fact, fibrotic intimal hyperplasia, endothelial dysfunction, occlusive vasculopathy are common features of Raynaud's phenomenon (RP), DUs, SRC and PAH (28). For this reason, it could be hypothesized that the increased RRI may represent a clinical biomarker of renal vascular injury. As far as we know, no studies focusing on PAH, RRI and renal function have been performed in SSc patients. In our population, PAH patients showed, over the time, a reduction of GFR and increase of  $\Delta$ RRI. In an observational study on 179 PAH patients, mainly affected by idiopathic PAH, in a follow-up of almost 3 year, our data were confirmed with a GFR mean reduction of 0.85 mL/min/1.73 m<sup>2</sup> per year. This suggests that the right heart failure might induce further renal hypo-perfusion with congestion, thus promoting renal injury and eGFR decrease (29). However, several studies have also shown that cardiac output and/or right atrial pressures are hemodynamic parameters are related to eGFR reduction in various pulmonary hypertension groups.

Consequently, the renal failure was associated with a higher mortality in PAH patients (30). Furthermore, other factors (venous congestion, inflammatory endothelial dysfunction, vasoconstrictive state, endothelin-1, interleukin-6, angiotensin and other molecules) can be involved to renal worsening correlated to PAH (30). Since PAH is a hemodynamic disease, chronic alterations of pulmonary perfusion can contribute to the reduction of the renal perfusion with slow GFR decline and increased intrarenal stiffness. The VEDOSS patients did not show any difference in RRI values when compared to those affected by an overt disease. Since RRI is increased for renal vasospasm like to Raynaud's phenomenon and proliferative obliterative vasculopathy, we can suppose that renal vascular damage is present also in very early stages of disease for renal vasospasm.

In our study 36.5% and 3.5% of patients were respectively diagnosed at baseline with systemic hypertension and diabetes. Although RRI is high in hypertensive and diabetic patients, in our study population eGFR medium was 97.5 (80.2-118.7) mL/min/1.73 m<sup>2</sup>. It is well known that systemic hypertension and diabetes are comorbidities leading to chronic kidney failure due to arterial stiffness is associated with eGFR reduction (31). In diabetes, the rapid increase of RRI is negatively correlated with eGFR. In our study,  $\Delta$ RRI changes were more evident in SSc patients with a non-pathological value of RRI than with pathological RRI at baseline. It may be hypothesized that SSc renal vasculopathy may determine an independent chronic and slow process increasing intrarenal resistances, as previously suggested (13).

A reduction of RRI has been previously demonstrated in the interlobar and cortical arteries after iloprost infusion with improvement of the renal blood flow. This evidence suggested that a stable prostacyclin analogue might be useful for treatment of SSc renal vasospasm (32). At baseline and during the follow-up, SSc patients were treated with several drugs classes. However,  $\Delta$ RRI increased significantly in patients treated with CCB or iloprost, compared to patients who did not receive these drugs. On the contrary, patients exposed to sildenafil showed a significantly lower  $\Delta$ RRI increase over time in comparison to sildenafil non-exposed patients.

Our study confirms that RRI and its variation in time are a reliable marker of SSc renal vasculopathy and other extra-renal compartments. . For the first time we demonstrated change of RRI was associated to NVC damage progression and new onset PAH. In addition significant changes of RRI are present in SSc patients treated with vasodilators and, in particular, in SSc patients treated with sildenafil.

Therefore, RRI might become either a useful tool in practice for patient's renal follow up but also a promising outcome measure for SSc related vasculopathy as well. The IRR utility should be confirmed in prospective studies and in randomized clinical trials.

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**Table 1.** Demographic and clinical features of systemic sclerosis patients at baseline

Age, years – median (IQR)	57 (48-67)
Male gender - n (%)	29 (12.6)
Smoke exposure - n (%)	30 (13.0)
Time from RP onset, years– median (IQR)	10 (4-20)
Time from disease onset, years – median (IQR)	6 (2-11)
Very early systemic sclerosis (VEDOSS) patient - n (%)	30 (13.0)
Cutaneous subset: sine scleroderma / limited / diffuse	33 (14.3) / 132 (57.4) / 65 (28.3)
mRSS – median (IQR)	5 (0-11)
Digital ulcer history/presence - n (%)	88 (38.3)
Late NVC pattern - n (%)	64 (27.8)
PAH - n (%)	13 (5.7)
sPAP – median (IQR)	27 (23-31)
Telangiectasias – n (%)	52 (22.6)
ILD - n (%)	63 (27.4)
Dyspnea - n (%)	71 (30.9)
%FVC – mean (SD)	102 (21)
% DLCO – mean (SD)	74 (18)
Upper GI symptoms - n (%)	152 (66.1)
Lower GI symptoms - n (%)	28 (12.2)
Arthritis - n (%)	32 (13.9)
Tendon friction rubs - n (%)	18 (7.8)
History of SRC - n (%)	2 (0.9)
Increase of CRP - n (%)	22 (9.6)
Increase of ESR - n (%)	58 (25.5)
ACA positivity - n (%)	117 (50.9)
Sc170 positivity - n (%)	81 (35.2)
RNA polymerase III positivity - n (%)	13 (5.7)



Creatinine Clearance – median (IQR)	97.50 (80.21-118.75)
RRI – mean (SD)	0.68 (0.07)

mRSS= modified Rodnan Skin Score; PAP= pulmonary arterial pressure; FVC= forced vital capacity; DLCO = lung diffusion for carbone oxyde; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; NTproBNP= N terminal pro-B natriuretic peptide; NYHA= New York Heart Association; RRI= renal resistive index; IQR=interquartile range; DU=digital ulcer; PAH= pulmonary arterial hypertension; ILD= interstitial lung disease; SRC= scleroderma renal crisis; GI= gastrointestinal; NVC= nailfold videocapillaroscopy

**Table 2.** Changes of features of SSc disease at follow-up

Change in mRSS – mean (SD)	+0.62 (3.98)
New onset of DU - n (%)	16 (7.0)
Worsening of NVC pattern- n (%)	25 (10.9)
New onset of PAH - n (%)	4 (1.7)
Change in sPAP – mean (SD)	1.24 (9.15)
New onset of Telangectasias – n (%)	10 (4.3)
New onset of ILD - n (%)	10 (4.3)
New onset of Dyspnea - n (%)	35 (15.2)
Change in %FVC – mean (SD)	-1.50 (15.09)
Change in DLCO – mean (SD)	-6.32 (13.33)
New onset of SRC - n (%)	5 (2.2)
Change in Creatinine Clearance – mean (SD)	-9.36 (18.58)
Change in RRI – mean (SD)	0.02 (0.05)

CRP= C-reactive protein; ESR=erythrocyte sedimentation rate; mRSS= modified Rodnan Skin Score; PAP= pulmonary arterial pressure; FVC= forced vital capacity; DLCO = lung diffusion for carbone oxyde; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; NTproBNP= N terminal pro-B natriuretic peptide; NYHA= New York Heart Association; RRI= renal resistive index; IQR=interquartile range. DU=digital ulcer; PAH= pulmonary arterial hypertension; ILD= interstitial lung disease; SRC= scleroderma renal crisis; GI= gastrointestinal; NVC= nailfold videocapillaroscopy

**Table 3.** Change of RRI and new onset of disease complication

	$\Delta$ RRI		P
	Yes	No	
New onset of DU - n (%)	0.05 $\pm$ 0.06	0.02 $\pm$ 0.05	0.059
Worsening of NVC pattern- n (%)	0.04 $\pm$ 0.04	0.03 $\pm$ 0.05	0.707
New onset of PAH - n (%)	0.08 $\pm$ 0.02	0.03 $\pm$ 0.05	<b>0.038*</b>
New onset of Telangectasias – n (%)	0.02 $\pm$ 0.05	0.03 $\pm$ 0.05	0.307
New onset of ILD - n (%)	0.04 $\pm$ 0.04	0.03 $\pm$ 0.05	0.512
New onset of Dyspnoea - n (%)	0.03 $\pm$ 0.06	0.02 $\pm$ 0.05	0.423
New onset of SRC - n (%)	0.04 $\pm$ 0.06	0.03 $\pm$ 0.05	0.535

DU=digital ulcer; PAH= pulmonary arterial hypertension; ILD= interstitial lung disease; SRC= scleroderma renal crisis; GI= gastrointestinal; NVC= nailfold videocapillaroscopy;  $\Delta$ RRI= change in renal resistive index

**Table 4.** Drugs therapy in SSc patients

	Treated during the study period	Treated at baseline	Newly treated during follow-up	Never treated
Sildenafil – n (%)	52 (22.6)	27 (11.7)	25 (10.9)	174 (75.7)
Bosentan – n (%)	85 (35.7)	64 (27.8)	21 (9.1)	143 (62.2)
Calcium Channel blockers – n (%)	131 (56.5)	113 (49.1)	18 (7.8)	96 (41.7)
Statins – n (%)	45 (19.1)	22 (9.6)	23 (10.0)	181 (78.7)
Iloprost – n (%)	99 (42.6)	94 (40.9)	5 (2.2)	128 (55.7)
PGE – n (%)	49 (20.9)	37 (16.1)	12 (5.2)	177 (77.0)
Steroids – n (%)	58 (23.9)	49 (21.3)	9 (3.9)	171 (74.3)
ARB – n (%)	41 (17.8)	26 (11.3)	15 (6.5)	185 (80.4)
Beta Blockers – n (%)	16 (7.0)	4 (1.7)	12 (5.2)	209 (90.9)
ACEi – n (%)	48 (20.9)	33 (14.3)	15 (6.5)	177 (77.0)
Immunosuppressants – n (%)	54 (23.5)	32 (13.9)	22 (9.6)	171 (74.3)

ΔARRI= change in renal resistive index

**Table 5.** Effect of drugs on  $\Delta$ RRi over the follow-up period

	$\Delta$ RRi				p value from Student T test		
	Treated during the study period	Treated at baseline	Newly treated during follow-up	Never treated	Ever vs never	BL vs never	Newly vs ever
Sildenafil	0.01±0.05	0.00 ± 0.05	0.02 ± 0.058	0.03 ± 0.05	0.028*	0.009*	0.582
Bosentan	0.02 ± 0.06	0.03 ± 0.05	0.01 ± 0.06	0.03 ± 0.05	0.681	0.664	0.090
Calcium Channel blockers	0.03 ± 0.05	0.03 ± 0.06	0.03 ± 0.04	0.02 ± 0.04	0.027*	0.033*	0.477
Statins	0.03 ± 0.05	0.03 ± 0.04	0.03 ± 0.06	0.03 ± 0.05	0.877	0.753	0.983
Iloprost	0.03 ± 0.05	0.03 ± 0.05	0.06 ± 0.06	0.02 ± 0.05	0.033*	0.088	0.084
Alprostadil	0.02 ± 0.05	0.02 ± 0.05	0.03 ± 0.06	0.03 ± 0.05	0.202	0.189	0.845
Steroids	0.03 ± 0.06	0.02 ± 0.06	0.03 ± 0.05	0.03 ± 0.05	0.797	0.617	0.858
Angiotensin Receptor blockers	0.02 ± 0.05	0.02 ± 0.05	0.02 ± 0.07	0.03 ± 0.05	0.416	0.698	0.418
Beta Blockers	0.03 ± 0.06	0.02 ± 0.06	0.03 ± 0.07	0.03 ± 0.06	0.896	0.775	0.952
Angiotensin converting enzyme inhibitors	0.02 ± 0.06	0.02 ± 0.05	0.01 ± 0.05	0.03 ± 0.05	0.527	0.824	0.165
Immunosuppressants	0.02 ± 0.06	0.02 ± 0.06	0.02 ± 0.06	0.06 ± 0.05	0.117	0.148	0.275

$\Delta$ RRi= change in renal resistive index

**Supplement Table 1** – Predictors of pulmonary arterial hypertension onset

	Univariate regression HR (95% CI)	P value	Multivariate regression HR (95% CI)	P value
Age	1.061 (0.972-1.158)	0.185		
Male gender	0.042 (0.000-170688)	0.682		
Time from RP onset	1.078 (0.998-1.165)	0.056		
Time from disease onset	1.077 (1.006-1.154)	0.034*	1.082 (0.947-1.236)	0.248
Established SSc versus Very early systemic sclerosis (VEDOSS) patient	24.35 (0.000-19546)	0.645		
Cutaneous subset limited	57.9 (0.018-184)	0.324		
mRSS	0.963 (0.807-1.149)	0.677		
Digital ulcer history/presence	1.569 (0.089-4.541)	0.653		
Late NVC pattern	1.262 (0.071-8.872)	0.850		
sPAP	1.054 (0.967-11253)	0.443		
Telangiectasias	96.563 (0.001-1206)	0.443		
ILD	0.594 (0.061-5.787)	0.654		
Dyspnoea	5.240 (0.540-50.805)	0.153		
%FVC	1.010 (0.964-1.057)	0.679		
%DLCO	0.948 (0.896-1.004)	0.067		
Increase of ESR	2.112 (0.297-15.030)	0.455		
ACA positivity	6.131 (0.612-61.379)	0.123		
Scl70 positivity	0.286 (0.029-2.823)	0.287		
Creatinine Clearance	0.996 (0.962-1.030)	0.805		
Change in mRSS	1.000 (0.775-1.289)	0.999		
Change in sPAP	1.082 (1.038-1.128)	<0.001*	1.076 (1.022-1.134)	0.006*
Change in RRI	7.127 (0.996-9.101)	0.050*	0.385 (0.000-1870)	0.961
Change in %FVC	0.990 (0.923-1.063)	0.789		
Change in %DLCO	0.944 (0.887-1.016)	0.123		
Change in Creatinine Clearance	0.961 (0.918-1.006)	0.086		
New onset of Dyspnoea	2.105 (0.189-23.405)	0.545		
New telangiectases	22.54 (0.000-3662)	0.795		
New DU	0.044 (0.000-69584)	0.712		

mRSS= modified Rodnan Skin Score; PAP= pulmonary arterial pressure; FVC= forced vital capacity; DLCO = lung diffusion for carbone oxyde; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; NTproBNP= N terminal pro-B natriuretic peptide; NYHA= New York Heart Association; RRI= renal resistive index; IQR=interquartile range; DU=digital ulcer; PAH= pulmonary arterial hypertension; ILD= interstitial lung disease; SRC= scleroderma renal crisis; GI= gastrointestinal; NVC= nailfold videocapillaroscopy

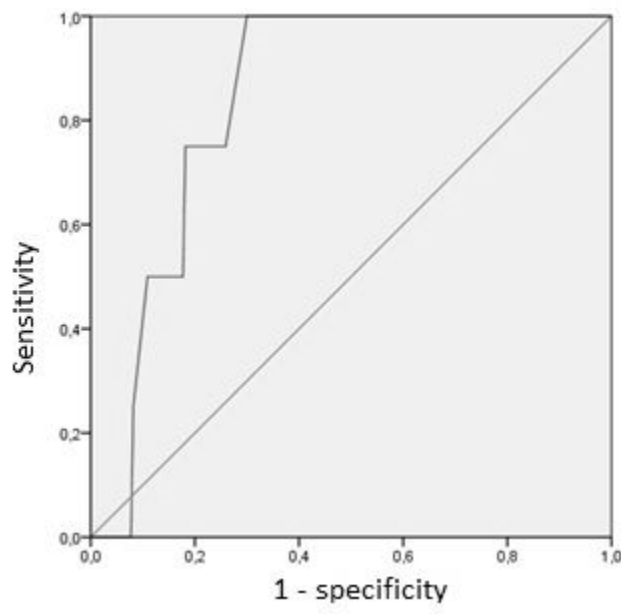


Figure 1. ROC curve for  $\Delta$ RRI as predictor of new onset PAH  
89x82mm (96 x 96 DPI)