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Tricuspid Annular Plane Systolic Excursion/Systolic Pulmonary Artery Pressure Ratio and Cardiorenal Syndrome Type 2 in the Systemic Sclerosis EUSTAR Cohort

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Objective. The aim of the study was to evaluate the association between the tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio and estimated glomerular filtration rate (eGFR) and their association with mortality in the European Scleroderma Trials and Research (EUSTAR) cohort.

Methods. Patients with systemic sclerosis (SSc) from the EUSTAR database with TAPSE, sPAP, and parameters required to calculate eGFR were included. Logistic regression and Cox regression analysis were performed to evaluate TAPSE/sPAP as a risk factor for chronic kidney disease (CKD) and overall survival.

Results. A total of 2,370 patients with SSc were included; 284 (12%) patients had CKD stage 3a–5. TAPSE/sPAP (odds ratio [OR] 0.479; 95% CI 0.310–0.743; $P < 0.001$), arterial hypertension (OR 3.118; 95% CI 2.173–4.475; $P < 0.001$), diastolic dysfunction (OR 1.670; 95% CI 1.148–2.428; $P < 0.01$), and N-terminal pro-B-type natriuretic peptide (OR 1.165; 95% CI 1.041–1.304; $P < 0.01$) were associated with CKD stage 3a–5. TAPSE/sPAP ≤0.32 mm/mm Hg (hazard ratio [HR] 3.589; 95% CI 2.236–5.761; $P < 0.001$), eGFR <60 mL/min per 1.73 m^2 (HR 2.818; 95% CI 1.777–4.468; $P < 0.001$), and age (HR 1.782; 95% CI 1.348–2.356; $P < 0.001$) were the most significant predictive factors for all-cause mortality. A total of 276 patients with SSc had pulmonary hypertension (PH) confirmed by right heart catheterization, with 69 (25%) having CKD stage 3a–5. No difference was found in eGFR between patients with PH with reduced or normal cardiac index.

Conclusion. Reduced TAPSE/sPAP ratio is independently associated with CKD. TAPSE/sPAP ratio ≤0.32 mm/mm Hg and eGFR <60 mL/min per 1.73 m^2 are prognostic factors for all-cause mortality. In patients with SSc with PH, eGFR is independent by reduced cardiac output.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease associated with a high burden of morbidity and mortality due to organ-based complications (1). SSc is characterized by an increased risk of subclinical and overt cardiopulmonary involvement, including heart failure (HF) (2,3). Pulmonary arterial hypertension (PAH) is a progressive disorder characterized by pulmonary vascular remodeling resulting in increased pulmonary vascular resistance and pulmonary artery pressure, chronic right ventricle (RV) pressure overload and RV dysfunction and, eventually, right HF (4). A common comorbidity in PAH is chronic kidney disease (CKD), with a reported prevalence ranging from 4% to 36% (5–9). CKD is often present at PAH diagnosis, and/or a decline in kidney function may occur in the course of the disease. CKD is strongly and independently associated with mortality in patients

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SIGNIFICANCE & INNOVATIONS

- The tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio is independently associated with chronic kidney disease (CKD), irrespective of left ventricle ejection fraction.
- Abnormal right ventricular–pulmonary arterial coupling is associated with cardiorenal syndrome type 2.
- In patients with pulmonary hypertension, CKD is not due to a reduced cardiac output.
- TAPSE/sPAP ≤0.32 mm/mm Hg and CKD are significant predictors for all-cause mortality.

with PAH (5–9). The complex and bidirectional interactions between heart and kidneys represent potential mechanisms explaining the high prevalence of kidney dysfunction in PAH. HF or CKD progression results in the activation of a cascade of events often accelerating cardiac and renal dysfunction. Cardiorenal syndrome (CRS) type 2 describes CKD as a consequence of chronic HF. A reduced cardiac output resulting in renal hypoperfusion has long been considered the only mechanism explaining the development of CKD in HF. However, more recently, several studies have shown that an increased right atrial pressure (RAP) leading to renal venous congestion and downstream impact on renal hemodynamics is involved in the loss of renal function in HF (10,11). Navaneethan et al. found a significant correlation between estimated glomerular filtration rate (eGFR) and RAP, but not between eGFR and cardiac index, in all groups of patients with pulmonary hypertension (PH) (7). In a previous study, we demonstrated that a reduced tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio is predictive of PH diagnosis and is associated with all-cause mortality in patients with SSc (12). The TAPSE/sPAP ratio is the noninvasive measure of right ventricular–pulmonary arterial (RV-PA) coupling and describes the continuum of the RV contractility adaptation to the afterload and, therefore, is strictly related to right heart hemodynamics (4,13). No study to date has investigated the TAPSE/sPAP ratio as a clinical index of renal dysfunction in patients with SSc.

Thus, the primary aim of the study was to evaluate the association between RV-PA coupling, assessed by TAPSE/sPAP ratio, and CKD, assessed by eGFR, in the SSc European Scleroderma Trials and Research (EUSTAR) cohort. The secondary aim of the study was to assess the association of TAPSE/sPAP ratio and eGFR with overall survival and mortality in the SSc EUSTAR cohort.

MATERIALS AND METHODS

Study design and population. A post hoc analysis of prospectively collected data from the multinational EUSTAR database was completed. The structure of the online database, the collected data set, and definitions of clinical variables have been described in detail previously (1,14).

All patients included in the EUSTAR database since 2010 (start of the online version), aged at least 18 years, fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria (15), and with at least one visit recording TAPSE, sPAP, and parameters required to calculate the eGFR (age, sex, and serum creatinine) were selected.

The TAPSE/sPAP ratio is not recorded in the EUSTAR database and was calculated for all patients with SSc as the ratio between TAPSE and sPAP measurements. sPAP was reported in millimeters of mercury, and a cutoff of >36 mm Hg was regarded as increased (16,17). TAPSE/sPAP ratio was expressed in millimeters per millimeters of mercury. A value of <0.55 mm/mm Hg was the cutoff selected to define the TAPSE/sPAP ratio reduced and suggestive of PH (12,16). A value of TAPSE/sPAP ratio ≤0.32 mm/mm Hg was the cutoff selected to define the intermediate-high risk of mortality (12,16).

eGFR is not recorded in the EUSTAR database and was calculated for all patients with SSc by the 2021 Chronic Kidney Disease Epidemiology Collaboration equation, expressed as a single equation as follows:

$$\text{eGFR} = 142 \times \min(S_{Cr}/k, 1)^{\alpha} \times \max(S_{Cr}/k, 1)^{-1.200} \times 0.9938^{\text{Age}} \times 1.012\,[\text{if female}],$$

where S_{Cr} is serum creatinine in mg/dL, age is in years, k is 0.7 for female and 0.9 for male individuals, α is –0.241 for female and –0.302 for male individuals, min indicates the minimum of S_{Cr}/k or 1, and max indicates the maximum of S_{Cr}/k or 1 (18,19).

CKD was defined as an eGFR <60 mL/min per 1.73 m^2 for more than 3 months (20). Patients were classified into CKD stages based on eGFR values of eGFR ≥60 mL/min per 1.73 m^2 (normal or stages 1–2), eGFR 45–59 mL/min per 1.73 m^2 (Stage 3a), eGFR 30–44 mL/min per 1.73 m^2 (Stage 3b), eGFR 15–29 mL/min per 1.73 m^2 (stage 4), and eGFR <15 mL/min per 1.73 m^2 (stage 5) (20).

All-cause mortality was evaluated in all included patients with SSc. The time interval (months) between the visit date recording TAPSE, sPAP, parameters required to calculate eGFR, and date of death was calculated.

The outcomes evaluated in this population were the association between the TAPSE/sPAP ratio and eGFR and the predictive value of TAPSE/sPAP ratio and eGFR for all-cause mortality.

Patients with right heart catheterization. Patients with SSc with available right heart catheterization (RHC) data (mean PAP [mPAP]) were selected among all patients included. PH was defined by a mPAP >20 mm Hg (16). Patients with SSc

with available cardiac index data were selected among patients with PH confirmed by RHC. Cardiac index was reported in liters per minute per meter squared, and a cutoff of <2.5 L/min per m^2 was used to define reduced cardiac index (16). Patients with PH were further classified in precapillary PH and postcapillary PH, according to the 2022 PH guidelines (16).

The outcomes evaluated in this population were as follows: 1) evaluate the difference in eGFR mean values between patients with and without PH; 2) evaluate the difference in eGFR mean values between patients with PH with and without a reduced cardiac index; and 3) evaluate the difference in eGFR mean values between patients with precapillary PH and postcapillary PH.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics version 26. Shapiro–Wilk was used to evaluate the normal distribution of data. Data were reported as mean ± SD; categorical data were represented as frequencies and proportions. Pearson's correlation coefficient was applied to evaluate the linear relationship between continuous variables. Student's *t*-test was used to evaluate between-group differences. Multiple regression analysis was used to evaluate the correlation between eGFR and independent variables (TAPSE, sPAP, TAPSE/sPAP ratio, left ventricle ejection fraction [LVEF]).

Univariate and multivariate binary logistic regression analyses with odds ratio (OR) and 95% confidence interval (CI) were performed to analyze the association between dependent variable (eGFR [<60 versus ≥60 mL/min per 1.73 m^2]) and independent variables (TAPSE, sPAP, TAPSE/sPAP ratio [mm/mm Hg], arterial hypertension [yes or no], LVEF [%], diastolic dysfunction [DD; yes or no], N-terminal pro-B-type natriuretic peptide [NT-proBNP; pg/mL], disease subset [limited cutaneus SSc; lcSSc]/diffuse cutaneus SSc; dcSSc]).

Kaplan–Meier curves and log-rank test were used to illustrate and compare the survival difference between different risk groups. Univariate Cox regression analysis was used to identify the independent prognostic factors for overall survival. Multivariate Cox regression analysis was performed on the significant variables in univariate Cox regression analysis. Hazard ratios (HRs) and 95% CIs were reported. All continuous variables were standardized with Z-score. Listwise deletion was used to handle missing data. Moreover, the multivariate imputation by chained equations was used to handle missing data (we used the function mice of the R package mice). The response variable eGFR was not used in the prediction. Five imputed data sets were produced. A *P* of less than 0.05 was considered statistically significant for all tests.

RESULTS

Within the EUSTAR database, 2,370 patients with SSc met the inclusion criteria for this study. Demographic and clinical characteristics of patients with SSc are shown in Table 1. TAPSE/sPAP ratio mean value was 0.84 ± 0.30 mm Hg. Serum creatinine and eGFR mean values were 0.86 ± 0.51 mg/dL and 86 ± 22 mL/min per 1.73 m^2, respectively. In total, 2,086 (88%) patients had an eGFR of ≥60 mL/min per 1.73 m^2, and 284 (12%) patients had CKD stage 3a–5.

Evaluation of the association of TAPSE/sPAP ratio with eGFR. A slightly positive correlation was found between eGFR and TAPSE/sPAP ratio (r = 0.271, $P < 0.001$) (Figure 1A), TAPSE (r = 0.137, $P < 0.001$), and LVEF (r = 0.104, $P < 0.001$); a slightly negative correlation was observed between eGFR and sPAP (r = –0.253, $P < 0.001$). A slightly positive correlation was found between forced vital capacity (FVC) and TAPSE/sPAP ratio (r = 0.238, $P < 0.001$). On multiple linear regression analysis,

Table 1. Demographic and clinical characteristics of 2370 patients with systemic sclerosis*

Characteristics	Results	N
Age, years	62 ± 14	2,370
Male	388 (16.4)	2,370
Disease duration, years	14 ± 10	2,063
lcSSc/dcSSc	1,386 (70.7)/575 (29.3)	1,961
ACA	761 (43.7)	1,742
ATA	580 (32.9)	1,763
ARA	134 (9.9)	1,360
mRSS	6 ± 7	1,816
Digital ulcers history	981 (44.5)	2,206
FVC, % predicted	92 ± 22	2,065
FVC <70% predicted	294 (14.2)	2,065
DL_{CO}, % predicted	66 ± 23	1,962
Interstitial lung disease	768 (53.9)	1,425
Arterial hypertension	623 (27.4)	2,274
LVEF, %	60.8 ± 6.6	2,164
LVEF <50%	74 (3.4)	2,164
Diastolic dysfunction	574 (28.5)	2,011
TAPSE, mm	21.8 ± 4.2	2,370
sPAP, mm Hg	30 ± 14	2,370
sPAP >36 mm Hg	452 (19.1)	2,370
TAPSE/sPAP, mm/mm Hg	0.84 ± 0.30	2,370
TAPSE/sPAP <0.55 mm/mm Hg	406 (17.1)	2,370
TAPSE/sPAP ≤0.32 mm/mm Hg	134 (5.7)	2,370
NT-proBNP, pg/mL	636 ± 3,534	1,486
Serum creatinine, mg/dL	0.86 ± 0.51	2,370
eGFR, mL/min per 1.73 m^2	86 ± 22	2,370
eGFR ≥90 mL/min per 1.73 m^2	1,216 (51.3)	2,370
eGFR 60–89 mL/min per 1.73 m^2	870 (36.7)	2,370
CDK Stage 3	242 (10.2)	2,370
CDK stage 4	27 (1.1)	2,370
CDK stage 5	15 (0.6)	2,370

* Percentages are calculated on the number of available data. Values are the mean ± SD or n (%) unless indicated otherwise. ACA = anti-centromere antibodies; ARA = anti-RNA polymerase III antibodies; ATA = anti-topoisomerase I antibodies; CKD = chronic kidney disease; DL_{CO} = diffusing capacity of the lungs for carbon monoxide; dsSSc = diffuse cutaneous systemic sclerosis; eGFR = estimated glomerular filtration rate; FVC = forced vital capacity; lcSSc = limited cutaneous systemic sclerosis; LVEF = left ventricular ejection fraction; mRSS = modified Rodnan skin score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion.

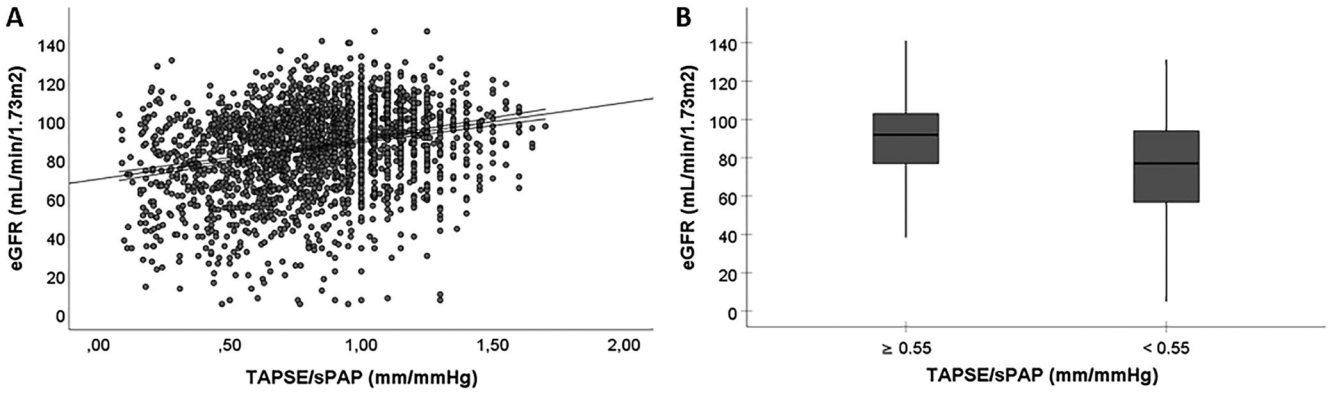

Figure 1. Tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio and estimated glomerular filtration rate (eGFR) in systemic sclerosis patients. **(A)** Correlation between TAPSE/sPAP ratio and eGFR; **(B)** eGFR in patients with and without TAPSE/sPAP ratio <0.55 mm/mm Hg.

eGFR was significantly correlated with TAPSE/sPAP ratio (β coefficient = 0.183; $P < 0.001$), sPAP (β coefficient = –0.092; $P < 0.05$), and LVEF (β coefficient = 0.072; $P < 0.01$). No correlation was found between eGFR and TAPSE (β coefficient = –0.022; $P = 0.505$). The eGFR mean value was significantly lower in patients with SSc with sPAP >36 mm Hg than in patients with SSc with sPAP ≤36 mm Hg (74 ± 23 mL/min per 1.73 m^2 versus 89 ± 21 mL/min per 1.73 m^2; $P < 0.001$) and in patients with SSc with TAPSE/sPAP <0.55 mm/mm Hg than in patients with SSc with TAPSE/sPAP ≥0.55 mm/mm Hg (74 ± 24 mL/min per 1.73 m^2 versus 89 ± 21 mL/min per 1.73 m^2; $P < 0.001$) (Figure 1B).

The eGFR mean value was significantly lower in patients with SSc with arterial hypertension than in normotensive patients (75 ± 23 mL/min per 1.73 m^2 versus 91 ± 20 mL/min per 1.73 m^2; $P < 0.001$). In patients with SSc with DD, eGFR mean value was significantly lower than in patients with normal diastolic function (78 ± 23 mL/min per 1.73 m^2 versus 90 ± 21 mL/min per 1.73 m^2; $P < 0.001$). The eGFR mean value was significantly lower in patients with lcSSc than in patients with dcSSc (84 ± 22 mL/min per 1.73 m^2 versus 91 ± 22 mL/min per 1.73 m^2; $P < 0.001$) and in patients with SSc with anticentromere antibodies (ACA) than in patients with SSc with antitopoisomerase I antibodies (ATA) (83 ± 20 mL/min per 1.73 m^2 versus 92 ± 21 mL/min per 1.73 m^2; $P < 0.001$). The eGFR mean value was significantly lower in patients with SSc with anti-RNA polymerase III antibodies (ARA) than in patients with SSc with ATA (82 ± 24 mL/min per 1.73 m^2 versus 92 ± 21 mL/min per 1.73 m^2; $P < 0.001$). No difference was found in eGFR mean value between patients with SSc with ACA and ARA.

The univariate binary logistic regression analysis showed that TAPSE (OR 0.662; 95% CI 0.583–0.752; $P < 0.001$), sPAP (OR 1.572; 95% CI 1.426–1.734; $P < 0.001$), TAPSE/sPAP ratio (OR 0.496; 95% CI 0.434–0.566; $P < 0.001$), arterial hypertension (OR 3.959; 95% CI 3.069–5.107; $P < 0.001$), LVEF (OR 0.761; 95% CI 0.673–0.860; $P < 0.001$), DD (OR 2.468; 95% CI 1.913–3.184; $P < 0.001$), NT-proBNP (OR 1.317; 95% CI 1.034–1.678; $P < 0.05$), and lcSSc (OR 1.580; 95% CI 1.154–2.163; $P < 0.01$) were significantly associated with CKD stage 3a–5 (Table 2). The multivariate binary logistic regression analysis showed that only TAPSE/sPAP ratio (OR 0.479; 95% CI 0.310–0.743; $P < 0.001$), arterial hypertension (OR 3.118; 95% CI 2.173–4.475; $P < 0.001$), DD (OR 1.670; 95% CI 1.148–2.428; $P < 0.01$), and NT-proBNP (OR 1.165; 95% CI 1.041–1.304; $P < 0.01$) were significantly associated with CKD stage 3a–5 (Table 2). The pooled results obtained from the analysis of the five imputed data sets showed that TAPSE/sPAP ratio (OR 0.621; 95% CI 0.457–0.843; $P < 0.01$), arterial hypertension (OR 3.105; 95% CI 2.377–4.057; $P < 0.001$), DD (OR 1.707; 95% CI 1.298–2.245; $P < 0.001$), lcSSc (OR 1.589; 95% CI 1.141–2.213; $P < 0.01$), and LVEF (OR 0.876; 95% CI 0.768–0.998; $P < 0.05$) were significantly associated with CKD stage 3a–5 (Table 2).

Mortality. All-cause mortality was analyzed in 2,271 (95.8%) patients with SSc, after excluding 99 (4.2%) patients lost at follow-up. Ninety-six (4.2%) patients died after a follow-up of 24 ± 21 months. Kaplan–Meier curves showed a higher mortality in patients with SSc with a TAPSE/sPAP ratio ≤0.32 mm/mm Hg (log-rank $\chi^2 = 85.8$, $P < 0.001$) (Figure 2A), in patients with SSc with eGFR <60 mL/min per 1.73 m^2 (log-rank χ^2 68.6, $P < 0.001$) (Figure 2B), in patients with SSc with FVC <70% predicted (log-rank χ^2 23.7, $P < 0.001$), and in patients with SSc with LVEF <50% (log-rank χ^2 6.8, $P < 0.05$). In univariate Cox regression analysis, TAPSE/sPAP ratio ≤0.32 mm/mm Hg (HR 6.302; 95% CI 4.030–9.855; $P < 0.001$), eGFR <60 mL/min per 1.73 m^2 (HR 4.826; 95% CI 3.196–7.288; $P < 0.001$), FVC <70% predicted (HR 2.998; 95% CI 1.954–4.600; $P < 0.001$), LVEF <50% (HR 2.828; 95% CI 1.421–5.627; $P < 0.01$), age (HR 1.948; 95% CI 1.532–2.476; $P < 0.001$), and dcSSc (HR 2.030; 95%

Table 2. Univariate and multivariate binary logistic regression analysis with listwise deletion (n = 1,486) and multiple imputation (n = 2,370) in patients with systemic sclerosis with categorization of estimated glomerular filtration rate in two groups: <60 vs. ≥60 mL/min per 1.73 m^2*

	Univariate analysis		Multivariate analysis (n = 1,486)		Multivariate analysis (n = 2,370)	
Parameters	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
lcSSc	1.580 (1.154–2.163)	<0.01	1.045 (0.683–1.598)	0.840	1.589 (1.141–2.213)	<0.01
Arterial hypertension	3.959 (3.069–5.107)	<0.001	3.118 (2.173–4.475)*	<0.001	3.105 (2.377–4.057)	<0.001
LVEF	0.761 (0.673–0.860)	<0.001	0.897 (0.765–1.052)	0.181	0.876 (0.768–0.998)	<0.05
Diastolic dysfunction	2.468 (1.913–3.184)	<0.001	1.670 (1.148–2.428)	<0.01	1.707 (1.298–2.245)	<0.001
NT-proBNP	1.317 (1.034–1.678)	<0.05	1.165 (1.041–1.304)	<0.01	1.101 (0.994–1.219)	0.065
TAPSE	0.662 (0.583–0.752)	<0.001	1.015 (0.791–1.303)	0.907	0.971 (0.812–1.161)	0.750
sPAP	1.572 (1.426–1.734)	<0.001	0.898 (0.672–1.200)	0.467	1.056 (0.864–1.290)	0.596
TAPSE/sPAP	0.496 (0.434–0.566)	<0.001	0.479 (0.310–0.743)	<0.001	0.621 (0.457–0.843)	<0.01

* lcSSc = limited cutaneous systemic sclerosis; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion.

CI 1.346–3.061; $P < 0.01$) were predictive factors for all-cause mortality. In multivariate Cox regression analysis, TAPSE/sPAP ratio ≤0.32 mm/mm Hg (HR 3.589; 95% CI 2.236–5.761; $P < 0.001$), eGFR <60 mL/min per 1.73 m^2 (HR 2.818; 95% CI 1.777–4.468; $P < 0.001$), dcSSc (HR 2.680; 95% CI 1.717–4.185; $P < 0.001$), and age (HR 1.782; 95% CI 1.348–2.356; $P < 0.001$) were the most significant predictive factors for all-cause mortality (Table 3). The pooled results obtained from the analysis of the five imputed data sets was reported in Table 3.

Patients with RHC. RHC data were available in 394 patients with SSc. Hemodynamic parameters are reported in Table 4. A total of 276 (70.1%) patients with SSc had PH confirmed by RHC. The eGFR mean value was significantly lower in patients with PH than in patients without PH (76 ± 23 mL/min per 1.73 m^2 versus 82 ± 23 mL/min per 1.73 m^2; $P < 0.05$). In the group of patients with SSc with PH, the prevalence of CKD was 25% (n = 69).

Cardiac index data were available in 221 patients with SSc with PH confirmed by RHC. Of these, 58 (26.2%) patients had a cardiac index <2.5 L/min per m^2, and 58 (26.2%) patients had an eGFR <60 mL/min per 1.73 m^2. No difference was found in eGFR mean value between patients with PH with a reduced cardiac index and patients with PH with normal cardiac index (77 ± 24 mL/min per 1.73 m^2 versus 75 ± 23 mL/min per 1.73 m^2; $P = 0.734$).

Pulmonary arterial wedge pressure and PVR data were available only in 215 patients with SSc with PH. Of these, 169 (78.6%) patients with SSc had precapillary PH. No difference was found in eGFR mean value between patients with precapillary PH and patients with postcapillary PH (77 ± 22 mL/min per 1.73 m^2 versus 70 ± 22 mL/min per 1.73 m^2; $P = 0.065$).

DISCUSSION

This is the first study to analyze the relationship between the noninvasive measure of RV-PA coupling and renal dysfunction.

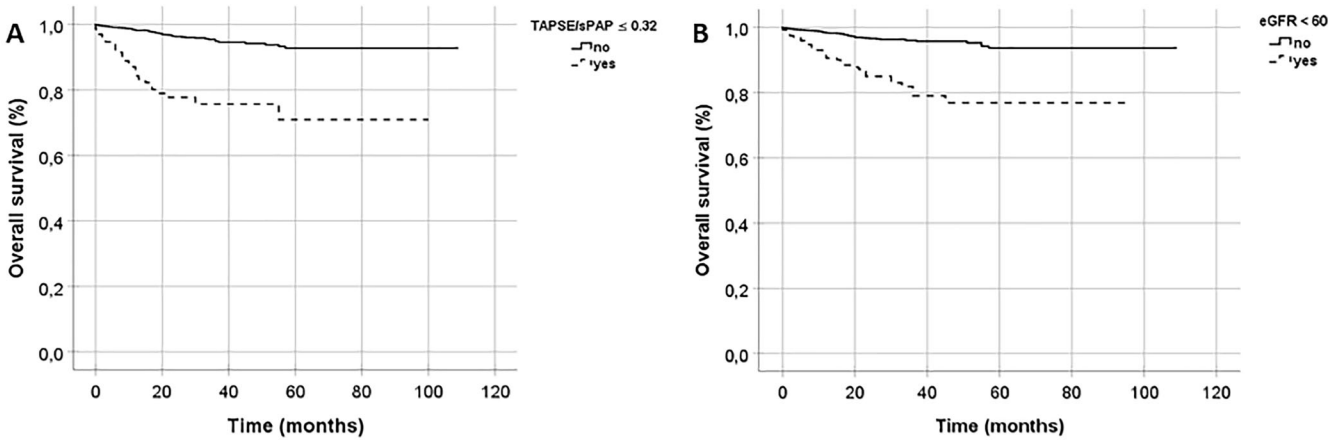

Figure 2. Overall survival in 2,271 patients with systemic sclerosis (SSc). **(A)** Overall survival in patients with SSc with tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio ≤0.32 mm/mm Hg (dotted line) and TAPSE/sPAP ratio >0.32 mm/mm Hg (continuous line); **(B)** overall survival in patients with SSc with estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 (dotted line) and eGFR ≥60 mL/min per 1.73 m^2 (continuous line).

Table 3. Univariate and multivariate Cox regression analysis for overall survival with listwise deletion (n = 2,065) and multiple imputation (n = 2,271) in patients with systemic sclerosis*

Parameters	Univariate analysis		Multivariate analysis (n = 2,065)		Multivariate analysis (n = 2,271)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
TAPSE/sPAP ≤0.32 mm/mm Hg	6.302 (4.030–9.855)	<0.001	3.589 (2.236–5.761)	<0.001	3.725 (2.290–6.060)	<0.001
eGFR <60 mL/min per 1.73 m^2	4.826 (3.196–7.288)	<0.001	2.818 (1.777–4.468)	<0.001	2.879 (1.796–4.616)	<0.001
FVC <70% predicted	2.998 (1.954–4.600)	<0.001	2.085 (1.317–3.300)	<0.01	1.880 (1.160–3.046)	<0.05
LVEF <50%	2.828 (1.421–5.627)	<0.01	1.259 (0.617–2.566)	0.527	1.131 (0.544–2.348)	0.739
Age	1.948 (1.532–2.476)	<0.001	1.782 (1.348–2.356)	<0.001	1.771 (1.336–2.348)	<0.001
Male sex	1.300 (0.786–2.152)	0.307	–	–	–	–
dcSSc	2.030 (1.346–3.061)	<0.01	2.680 (1.717–4.185)	<0.001	2.808 (1.785–4.417)	<0.001

* CI = confidence interval; dsSSc = diffuse cutaneous systemic sclerosis; eGFR = estimated glomerular filtration rate; FVC = forced vital capacity; HR = hazard ratio; LVEF = left ventricular ejection fraction; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion.

Our data, derived from a large cohort of patients with SSc, showed that the TAPSE/sPAP ratio was independently associated with CKD, and patients with SSc with a reduced TAPSE/sPAP ratio and CKD were characterized by a decreased survival. CKD was frequent in patients with SSc with PH, and the eGFR did not seem to depend on cardiac output.

Heart and kidneys are tightly linked, and the dysfunction in one organ may result in the dysfunction of the other. In CRS type 2, chronic HF results in the onset or progression of CKD. Renal congestion, rather than renal hypoperfusion, has been identified as the leading underlying cause for kidney dysfunction in HF (11). These mechanisms also apply to right HF due to PAH (21). Although RHC is the gold standard to directly measure right cardiac pressures and cardiac output, echocardiographic parameters can be used to estimate hemodynamic parameters that can be obtained from RHC. The TAPSE/sPAP ratio is a echocardiographic parameter of RV dysfunction strictly related to pulmonary and right heart hemodynamics (4,13).

This is the first study to show a positive linear correlation between TAPSE/sPAP ratio and eGFR. Patients with SSc with a TAPSE/sPAP ratio <0.55 mm/mm Hg had lower eGFR than patients with higher values. The 2022 PH guidelines include TAPSE/sPAP ratio <0.55 mm/mm Hg among signs suggestive of PH (16). Recently, we demonstrated that a TAPSE/sPAP ratio <0.55 mm/mm Hg was a predictive risk factor for PH confirmed by RHC in patients with SSc (12). These results seems to suggest that patients who are most likely to have PH may also have kidney dysfunction. In the present study, TAPSE/sPAP ratio was independently associated with CKD stages 3a–5 and was more strongly associated with CKD than NT-proBNP. To date, there are no specific diagnostic biomarkers for CRS. Biomarkers of cardiac and kidney injury may be useful to detect early cardiac or renal dysfunction in the clinical context of CRS (10). Natriuretic peptides (NPs), as biomarkers of myocardial wall stress, have both diagnostic and prognostic value in HF, PH, and CRS (10,16,22). Patients with CKD have higher NP levels (particularly NT-proBNP) not only due to reduced renal clearance but also because of chronic pressure/volume overload and CKD-associated cardiomyopathy (23). Patients with CRS have higher B-type natriuretic peptide (BNP) levels than patients with HF without renal impairment (24). TAPSE/sPAP ratio was a better predictive factor of PH diagnosis than NT-proBNP in our previous study (12). We may hypothesize that the TAPSE/sPAP ratio, detecting early mild right heart hemodynamic changes, could also be an index of renal dysfunction in the context of PH and CRS. Moreover, our results showed that TAPSE/sPAP ratio and DD were more strongly associated with CKD than LVEF. CKD has been associated with abnormal longitudinal strain parameters in patients with HF and preserved LVEF (25). DD has been associated with increased risk of CKD progression (26).

Table 4. Right heart catheterization parameters of 394 patients with systemic sclerosis*

Parameters	Results	N
mPAP, mm Hg	27 ± 11	394
mPAP >20 mm Hg	276 (70.1)	394
PAWP, mm Hg	11 ± 5	315
PVR, WU	3.6 ± 3.2	225
CO, L/min	4.7 ± 1.5	223
Cardiac index, L/min per m^2	3.1 ± 1	313
Cardiac index <2.5 L/min per m^2	83 (26.5)	313

* Values are in mean ± SD or n (%) unless indicated otherwise. CO = cardiac output; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; WU = Wood units.

TAPSE/sPAP ratio ≤0.32 mm/mm Hg and eGFR <60 mL/min per 1.73 m^2 were independently associated with all-cause mortality, even when adjusted for known risk factors for increased mortality in patients with SSc, including age, male sex, diffuse disease subset, FVC <70% of the predicted value, and LVEF <50% (1). Moreover, TAPSE/sPAP ratio ≤0.32 mm/mm Hg, eGFR <60 mL/min per 1.73 m^2, and age were the most significant predictive factors for mortality. In two previous distinct studies, we found that TAPSE/sPAP ratio ≤0.32 mm/mm Hg and eGFR <60 mL/min per 1.73 m^2 were associated with mortality in patients with SSc (12,27). The 2022 European Society of Cardiology/European Respiratory Society three-strata risk-

assessment tool includes TAPSE/sPAP ratio as a risk factor for death in patients with PAH (16), whereas the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0 risk score and its abridged version REVEAL Lite 2 include eGFR <60 mL/min per 1.73 m^2 as a prognostic factor in patients with PAH (28,29). Future studies are needed to evaluate these two parameters in a multiparametric risk-assessment tool to improve risk stratification in patients with SSc.

Our study also showed that patients with SSc with PH, irrespective if precapillary or postcapillary PH, had lower eGFR mean values than patients without PH. The prevalence of CKD in patients with SSc with PH confirmed by RHC was 25%. Our results are consistent with previous studies. Data from the REVEAL registry, including only patients with PAH, reported a prevalence of CKD of 28% (8). In all groups of patients with PH was found a prevalence of 36% (7). Moreover, in our study, no difference was found in eGFR between patients with PH with reduced or normal cardiac index. Bitker et al. showed that increased RAP and reduced cardiac index were both independently associated with a decline in renal function in 179 patients with PAH (9), whereas Navaneethan et al. found a significant correlation between eGFR and RAP but not between eGFR and cardiac index in 1,088 patients with all PH groups (7). Several studies reported no association between cardiac index and eGFR in HF, supporting the hypothesis that low cardiac output is not the primary driver for renal dysfunction in patients with HF (30–33). This seems to support our findings that a parameter strictly related to an abnormal right heart hemodynamics could also be a valuable index of kidney dysfunction. In patients with SSc with CRS type 2, the renal function should be monitored frequently because the vasoactive drugs, used to improve Raynaud's phenomenon, could reduce renal blood flow.

A major strength of the study is the large sample size. However, the study has some limitations. Patient selection was based on available data. Data about proteinuria and albuminuria and/or other functional or structural markers of kidney disease were not provided by the EUSTAR database. Therefore, patients with an eGFR of ≥90 and of 60–89 mL/min per 1.73 m^2 could not be further classified as having normal renal function or CKD stage 1 or 2. Data on pre-existing renal disease are not available in EUSTAR registry. Also, we did not have data on diabetes and other pre-existing comorbidities potentially involved in kidney dysfunction, and there were no data on therapy potentially affecting volume status, serum creatinine levels, and eGFR. Furthermore, biomarkers of CRS were not included in the EUSTAR database. The cause of death for patients with SSc was missing in many patients, and mortality due to PH was not registered in the EUSTAR database. Many RHC data were missing and RAP was not provided by the EUSTAR database.

In conclusion, our results show that TAPSE/sPAP ratio is an echocardiographic parameter associated with CKD in patients with SSc, independently of LVEF. Abnormal RV-PA coupling is associated with CRS type 2 in patients with SSc, irrespective of PH diagnosis. In a subgroup analysis of patients with SSc with PH confirmed by RHC, our data confirm that CKD is not due to a reduced cardiac output. Our results strengthen previous findings that TAPSE/sPAP ratio ≤0.32 mm/mm Hg and eGFR <60 mL/min per 1.73 m^2 are the most significant predictive factors for all-cause mortality in patients with SSc.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rosato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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