Original article

Estimated glomerular filtration rate is a marker of mortality in the European Scleroderma Trials and Research Group (EUSTAR) database

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Abstract

Objectives. The study aim was to evaluate the estimated glomerular filtration rate (eGFR), its association with clinical disease and its predictive ability with respect to mortality in SSc patients from the European Scleroderma Trials and Research Group (EUSTAR) database.

Methods. SSc patients from the EUSTAR database who had items required for the calculation of eGFR at a base-line visit and a second follow-up visit available were included. A cut-off eGFR value of 60 ml/min was chosen for all SSc patients, and 30 ml/min for those with scleroderma renal crisis (SRC). Cox regression and competing risk analysis were performed to evaluate the use of eGFR as a predictive factor of mortality.

Results. A total of 3650 SSc patients were included in this study. The median serum level of creatinine and the mean of eGFR were 0.8 mg/dl (interquartile range = 0.6–0.9) and 86.6 ± 23.7 ml/min, respectively. The eGFR was significantly lower in patients with pulmonary hypertension. Overall survival (OS) was significantly reduced in SSc patients with eGFR < 60 ml/min compared with patients with eGFR ≥ 60 ml/min [OS at 5 years 0.763 (95% CI: 0.700, 0.814) vs 0.903 (95% CI: 0.883, 0.919; $P < 0.001$)]. In multivariable analysis, OS was associated with male gender ($P < 0.01$), systolic pulmonary arterial pressure (sPAP) ($P < 0.001$) and eGFR ($P < 0.001$). The cumulative incidence of deaths due to SSc was associated with increased sPAP ($P < 0.001$) and reduced eGFR ($P < 0.05$). The OS at 5 years of 53 SRC patients was not significantly different between SSc patients with eGFR > 30 ml/min and those with eGFR < 30 ml/min.

Conclusion. eGFR represents a predictive risk factor for overall survival in SSc. The eGFR, however, does not represent a risk factor for death in SRC.

Key words: systemic sclerosis, glomerular filtration rate, scleroderma renal crisis, EUSTAR

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CLINICAL SCIENCE

Rheumatology key messages

- In SSc patients from the EUSTAR registry, the estimated glomerular filtration rate (eGFR) was normal or slightly reduced.
- The eGFR represented a predictive risk factor for mortality due to SSc and other causes in the overall cohort of patients with SSc.
- The eGFR was not found to represent a predictive risk factor for mortality in those SSc patients with scleroderma renal crisis.

Introduction

SSc is a CTD associated with a high risk of mortality [1]. In the past, one of the main causes of death has been scleroderma renal crisis (SRC) [2]. In SSc patients, SRC is the most recognized renal disease, but urinalysis abnormalities, abnormal renal vascular resistance indices and isolated reduced glomerular filtration rate (GFR) have also been reported [3]. In 461 SSc patients followed over 10 years, decreased GFR occurred in 11% of patients with lcSSc and in 8.6% of those with dcSSc [4].

Chronic kidney disease (CKD) is associated with 4% of deaths worldwide. Several studies report on the relationship between GFR and risk of adverse events in the general population [5]. The association between impaired renal function and mortality has not been assessed in SSc patients without SRC.

The aims of the study were (i) to evaluate the renal involvement in SSc patients assessed by estimated glomerular filtration rate (eGFR), (ii) to assess associations with specific clinical disease variables and laboratory findings, (iii) to evaluate the predictive role of eGFR on overall survival (OS) and mortality in SSc patients from the EULAR Scleroderma Trials and Research (EUSTAR) database.

Materials and methods

Study design

This study involved analysis of the multinational European Scleroderma Trials and Research Group (EUSTAR) database. Clinical information from patient visits are recorded prospectively using standardized data collection forms, including a unique identification number, dates of RP and first non-RP symptom onset (disease duration), clinical and demographic data, physical findings, and clinical and laboratory parameters [6]. All patients fulfilled the 2013 ACR/EULAR classification criteria and were grouped as dcSSc or lcSSc [7, 8]. Ethical approval for use of data from the EUSTAR database was obtained by each participating site. Written informed consent was obtained from the subjects. Their clinical records and information were anonymized prior to analysis. This study complies with the Declaration of Helsinki. All SSc patients from the EUSTAR registry with baseline visits between January 2004 and April 2018 and at least one follow-up visit were analysed. Patients were considered eligible for the study if they presented the following features at baseline: (1) availability of demographic items, clinical disease variables and date of SRC onset; (2) availability of data for calculation of eGFR (age, serum creatinine, sex and race) and (3) availability of vital status at the last observation and date and causes of death.

Estimated glomerular filtration rate

At baseline, eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, expressed as a single equation: GFR = 141 min $(sCr/k, 1)^{\alpha} \times$ max $(sCr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times$ 1.159 (if Afro-American), in which k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of sCr/k or 1, and max indicates the maximum of sCr/k or 1 [9].

CKD is defined by eGFR according to the Kidney Disease Improving Global Outcomes. Five stages of CKD are defined according to the value of the eGFR from the CKD-EPI creatinine equation: stage 1: eGFR > 90 ml/min/1.73 m^2; stage 2: eGFR 60–89 ml/min/1.73 m^2; stage 3a: eGFR 45–59 ml/min/1.73 m^2; stage 3b: eGFR 30–44 ml/min/1.73 m^2; stage 4: eGFR 15–29 ml/min/1.73 m^2; stage 5: eGFR < 15 ml/min/1.73 m^2. Stages 3a and 3b were grouped. CKD was defined as abnormalities of kidney function with estimated eGFR < 60 ml/min/1.73 m^2 present over 3 months [10].

Clinical characteristics

EUSTAR database data for the following clinical characteristics was included, based on definitions according to the EUSTAR database:

1. SSc subtype: SSc-specific antibodies (anti-topo I, anti-RNA polymerase III, anti-U1RNP and ACAs), skin disease assessed by the modified Rodnan skin score, digital ulcers, SRC and capillaroscopic patterns [6];
2. pulmonary hypertension (PH): a systolic pulmonary arterial pressure (sPAP) >30 mmHg on echocardiography;
3. arterial hypertension: systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg;

4. death: the exact date of death was reported. The cause of death was defined as due to SSc, other causes or unknown. It was not possible to establish from the EUSTAR database the cause of death due to specific SSc complications.

Outcomes

From this data we evaluated:

1. eGFR by CKD-EPI and its association with disease-specific variables.
2. the predictive role of eGFR for OS and mortality at 5 years due to SSc or other causes, based on the data from the EUSTAR database.
3. eGFR at onset of SRC and its predictive role on OS among SRC patients.

Statistical analysis

Data were summarized as mean (S.D.) or median and interquartile range (IQR); categorical data were represented as frequencies and proportions. One-way analysis of variance (Student's t-test) or analysis of variance was used to determine whether there was a statistical difference between the group means of eGFR. The Bonferroni correction was applied for multiple comparisons. The Pearson correlation coefficient was calculated to evaluate the overall linear relationship between eGFR and clinical variables. OS data were represented by Kaplan–Meier curves, and log-rank testing was used for statistical comparisons; Cox regression was used for multivariable analysis of risk factors. Hazard ratio (HR) and 95% CI were reported.

Cumulative incidence was used to evaluate cause-specific mortality. Cumulative incidence is defined as the probability that a particular event, such as occurrence of a particular disease, has occurred before a given time. Gray's test was used to evaluate the hypothesis of equality of cumulative incidence functions between two groups. Multiple cause-specific Cox proportional hazard regression models were fitted for multivariable analysis. A significance level of 0.05 was

TABLE 1 Patients' characteristics ($n = 3650$) at baseline

Demographic and clinical variables	Results	Number of patients with data
Male sex, n (%)	579 (15.9)	3650
Age, median (IQR), years	57.6 (13.4)	3650
White race, n (%)	3598 (98.6)	3650
Serum creatinine, median (IQR), mg/dl	0.8 (0.6–0.9)	3650
eGFR, mean (SD), ml/min	86.6 (23.7)	3650
dcSSc/lcSSc, n	972/1905	2877
Modified Rodnan Skin Score, median (IQR)	6 (3–11)	721
Disease duration (years from onset of first non-RP disease), median (IQR)	9.7 (4.9–16.4)	3281
Digital ulcers, n (%)	1618 (49.7)	3254
Pulmonary hypertension, n (%)	376 (14.6)	2579
Arterial hypertension, n (%)	876 (24.3)	3604
Autoantibody, n (%)		
ANA	2899 (96.9)	2991
ACA	1059 (38.4)	2756
Anti-topo I antibody	1026 (36.4)	2817
Anti-RNA polymerase III antibody	136 (6.8)	2001
Diastolic function abnormal	790 (31.8)	2486
Proteinuria	218 (7.4)	2951
Hypocomplementaemia	215 (10)	2158
DLCO % predicted, median (IQR)	65.9 ± 20.3	2593
FVC % predicted, median (IQR)	94.2 ± 22.5	2814
sPAP, median (IQR), mmHg	29 (25–35)	1951
Left ventricular ejection fraction, median (IQR), %	60 (60–65)	2397
Capillaroscopic scleroderma pattern, n (%)		
Early	487 (39.2)	1242
Active	266 (21.4)	1242
Late	489 (39.4)	1242

For numerical variables, median and interquartile range (IQR) are shown, and for nominal variables, the absolute and relative frequencies are shown. eGFR: estimated glomerular filtration rate; DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vitality capacity; RNA Pol III: RNA polymerase III antibodies; sPAP: systolic pulmonary arterial pressure.

used for all tests. Analysis was performed using R version 3.6.2 (https://www.R-project.org/).

Results

Baseline characteristics

We extracted 16 932 patients from the EUSTAR database. Of these, 3650 SSc patients met the inclusion criteria at the time of data extraction (28 May 2019). Of the 3650, 579 (15.9%) SSc patients were male and the mean age was 57.6 (13.4) years. The median (IQR) duration of follow-up was 1.9 (1.05–3.45) years. The median serum level of creatinine was 0.8 mg/dl (IQR 0.6–0.9) and the mean eGFR was 86.6 (23.7) ml/min. Demographic and clinical features are shown in Table 1. The included SSc patients were representative of the entire population, because there were no significant demographic or clinical differences between the SSc patients included and those excluded: male sex (15.9% *vs* 14.7%), age [57.6 (13.4) years *vs* 58.2 (14.4) years], digitals ulcers (49.7% *vs* 47.8%), PH (14.6% *vs* 20.9%) or arterial hypertension (24.3% *vs* 23.6%).

eGFR in subgroups of patients

In SSc patients with PH, the mean value of eGFR was significantly lower than in SSc patients without PH [76.4 (23.9) ml/min *vs* 88.4 (22.9) ml/min, $P < 0.001$]. In SSc patients with anti-topo I autoantibodies, the mean value of eGFR was 91.3 (24) ml/min significantly higher ($P < 0.001$) than in SSc patients with ACA (82.7 ± 20.8 ml/min) or anti-RNA polymerase III autoantibodies [81.3 (27.2) ml/min]. No significant difference in eGFR was observed between SSc patients with ACA and those with anti-RNA polymerase III autoantibodies. No significant ($P > 0.05$) differences in eGFR were observed between the capillaroscopic patterns: early 89.6 (22) ml/min, active 88.8 (23.4) ml/min and late 88.7 (25.2) ml/min.

OS analysis

Of the 3650 SSc patients included in this study, 226 SSc patients (6.2%) became deceased over the follow-up period of 1.9 (IQR = 1.05–3.45) years. Of the 226 deaths, 112 (49.6%) deaths were due to SSc and 114 (50.4%) deaths were due to other causes.

We assessed OS in SSc patients with eGFR ≤ 60 ml/min and SSc patients with eGFR > 60 ml/min. OS was significantly reduced in SSc patients with eGFR ≤ 60 ml/min as compared with SSc patients with eGFR > 60 ml/min [OS at 5 years 0.763 (95% CI: 0.700, 0.814) *vs* 0.903 (95% CI: 0.883, 0.919), $P < 0.001$] (Fig. 1A).

FIG. 1 The overall survival in 3650 SSc patients with estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD)
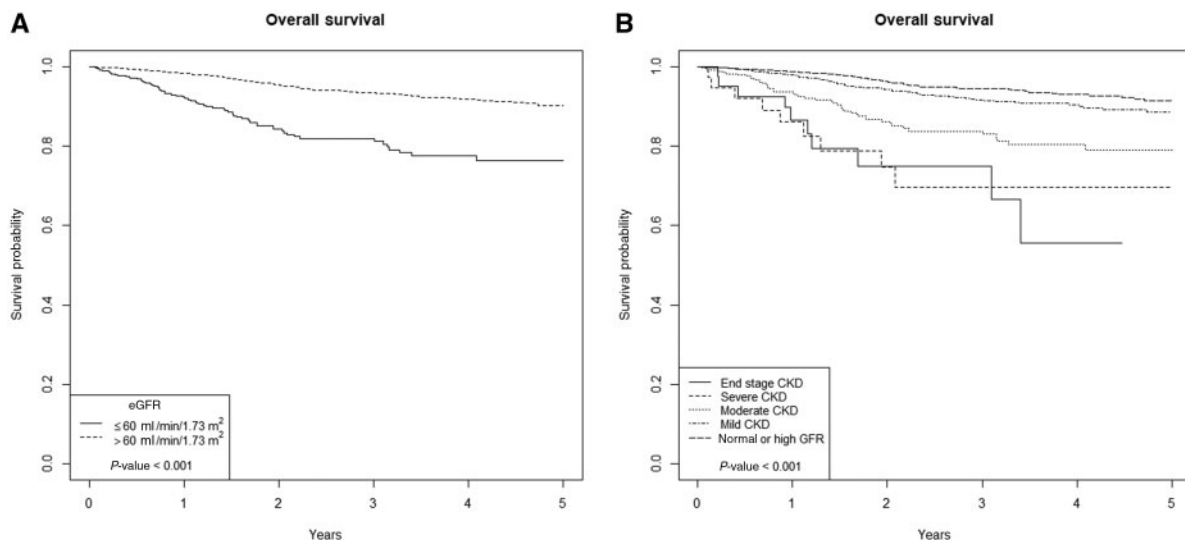
(**A**) Overall survival in SSc patients with eGFR ≤ 60 ml/min and eGFR > 60 ml/min. The overall survival is significantly ($P < 0.001$) lower in SSc patients with eGFR ≤ 60 ml/min (continuous line) than in SSc patients with eGFR > 60 ml/min (dotted line); (**B**) overall survival in five stages of CKD according to eGFR value. The overall survival is significantly ($P < 0.001$) lower in SSc patients with stages 3, 4 and 5 of CKD than in SSc patients with stages 2 and 1 of CKD.

Of the 3650 SSc patients, 1849 SSc patients (50.7%) were in stage 1 of CKD, 1325 patients (36.3%) were in stage 2 of CKD, 398 patients (10.9%) were in stage 3 of CKD, 38 patients (1%) were in stage 4 of CKD and 40 patients (1.1%) were in stage 5 of CKD. With reference to the five stages of CKD, the OS was as followed: the HR for stage 1 was 0.132 (95% CI: 0.068, 0.256, $P < 0.001$), the HR for stage 2 was 0.198 (95% CI: 0.102, 0.382, $P < 0.001$), the HR for stage 3 was 0.467 (95% CI: 0.237, 0.920, $P = 0.028$) and the HR for stage 4 was 0.885 (95% CI: 0.360, 2.179, $P = 0.792$). SSc patients with stages 1 and 2 CKD showed higher survival than those at other CKD stages (Fig. 1B).

In univariable Cox regression analysis, age (HR = 1.051, 95% CI: 1.039, 1.062; $P < 0.001$), male sex (HR = 1.895, 95% CI: 1.403, 2.559; $P < 0.001$), sPAP (HR = 1.049, 95% CI: 1.041–1.057, $P < 0.001$) and eGFR (HR = 0.978, 95% CI: 0.974, 0.983; $P < 0.001$) were associated with deaths due to SSc. In multivariable Cox regression analysis, deaths due to SSc were associated with male sex (HR = 1.840, 95% CI: 1.217, 2.782; $P < 0.01$), sPAP (HR = 1.039, 95% CI: 1.030, 1.048; $P < 0.001$) and eGFR (HR = 0.985, 95% CI: 0.978, 0.993; $P < 0.001$).

Cumulative incidence according to renal function stages

We evaluated the cumulative incidence of death due to SSc and other causes in SSc patients with eGFR ≤ 60 ml/min or eGFR > 60 ml/min. Deaths due to SSc ($n = 112$, 49.6%) were significantly ($P < 0.001$) higher in SSc patients with eGFR ≤ 60 ml/min than in SSc patients with eGFR > 60 ml/min (Fig. 2A). Renal dysfunction as a cause of death was not reported.
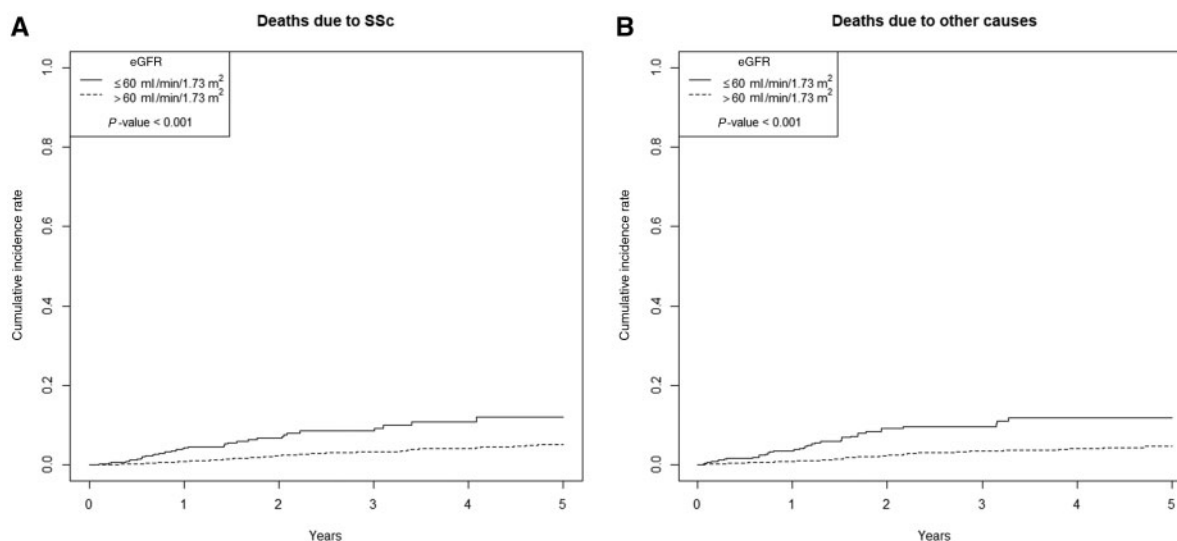
In addition, deaths due to others causes ($n = 114$, 50.4%) were significantly ($P < 0.001$) higher in SSc patients with eGFR ≤ 60 ml/min than in SSc patients with eGFR > 60 ml/min (Fig. 2B). We evaluated the cumulative incidence of death due to SSc and other causes in SSc patients with different stages of CKD.

Deaths due to SSc were significantly ($P < 0.001$) higher in SSc with stages 3a–5 of CKD ($n = 34$, 7.1%) than in SSc patients ($n = 78$, 2.5%) with stages 1 and 2 CKD (Fig. 3A). With reference to the five stages of CKD, the HR for stage 1 was 0.137 (95% CI: 0.054, 0.347, $P < 0.001$), the HR for stage 2 was 0.187 (95% CI: 0.073, 0.479, $P < 0.001$), the HR for stage 3 was 0.426 (95% CI: 0.164, 1.119, $P = 0.083$), and the HR for stage 4 was 0.977 (95% CI: 0.283, 3.377, $P = 0.971$).

Deaths due to other causes were significantly ($P < 0.001$) higher in SSc patients ($n = 37$, 7.8%) with stages 3a–5 CKD than in SSc patients ($n = 77$, 2.4%) with stages 1 and 2 CKD (Fig. 3B). With reference to the five stages of CKD, the HR for stage 1 was 0.127 (95% CI: 0.050, 0.325, $P < 0.001$), the HR for stage 2 was 0.209 (95% CI: 0.083, 0.530, $P < 0.001$), the HR for stage 3 was 0.509 (95% CI: 0.197, 1.320, $P = 0.165$), and the HR for stage 4 was 0.792 (95% CI: 0.213, 2.951, $P = 0.728$).

In univariable competing risk analysis, the baseline variables significantly predicting cumulative incidence of deaths due to SSc were age (HR = 1.029, 95% CI: 1.013, 1.044; $P < 0.001$), male sex (HR = 1.620, 95% CI: 1.038, 2.527; $P < 0.05$), sPAP (HR = 1.058, 95% CI: 1.047, 1.068; $P < 0.001$) and eGFR (HR = 0.980, 95% CI: 0.974, 0.987; $P < 0.001$). In multivariable competing risk analysis, cumulative incidence of deaths due to SSc was predicted

Fig. 2 Cumulative incidence of death due to SSc and other causes in 3650 SSc patients with estimated glomerular filtration rate (eGFR)

(**A**) Cumulative incidence due to SSc is significantly ($P < 0.001$) higher in SSc patients with eGFR ≤ 60 ml/min than in SSc patients with eGFR > 60 ml/min. (**B**) Cumulative incidence due to others causes is significantly ($P < 0.001$) higher in SSc patients with eGFR ≤ 60 ml/min than in SSc patients with eGFR > 60 ml/min.

FIG. 3 Cumulative incidence of death due to SSc and other causes in 3650 SSc patients with five stages of chronic kidney disease (CKD) according to the estimated value of glomerular filtration rate (eGFR)
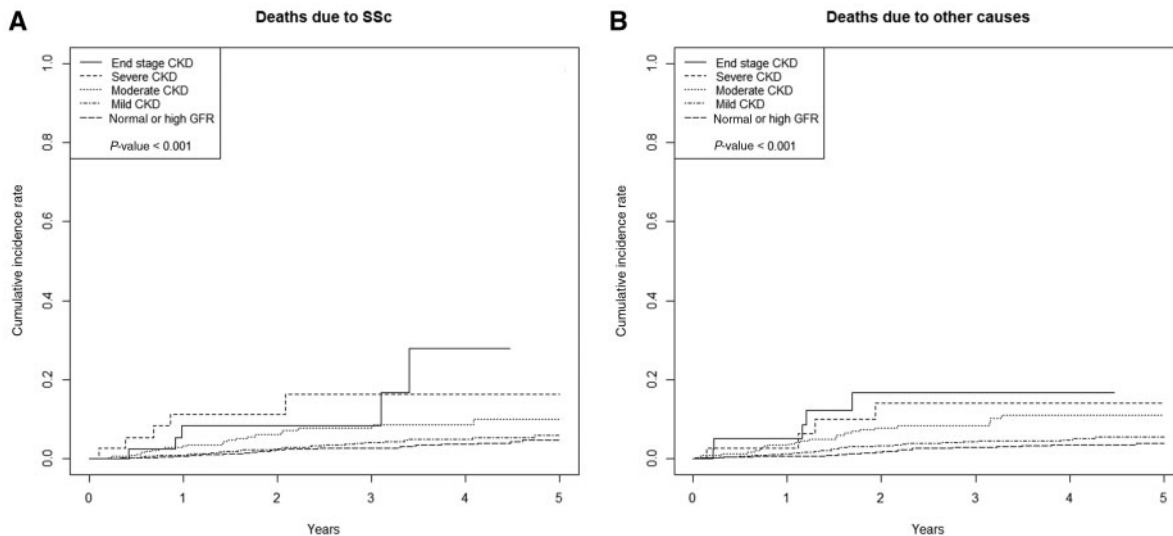
(**A**) Cumulative incidence due to SSc is significantly (*P* < 0.001) higher in SSc patients with stages 3, 4 and 5 of CKD than in SSc patients with stages 2 and 1 of CKD. (**B**) Cumulative incidence due to others causes is significantly (*P* < 0.001) higher in SSc patients with stages 5–4–3 of CKD than in SSc patients with stages 2 and 1 of CKD.

TABLE 2 Competing risk analysis: univariate and multivariable hazard ratio (HR) and 95% CI of deaths due to SSc and due to other causes

Demographic and clinical variables	Univariate analysis			Multivariable analysis		
	HR	**95% CI**	*P*-value	**HR**	**95% CI**	*P*-value
			Deaths due to SSc			
Sex (male)	1.620	1.038, 2.527	<0.036	1.257	0.655, 2.410	0.049
Age, years	1.029	1.013, 1.044	<0.001	0.995	0.971, 1.018	0.066
sPAP, mmHg	1.058	1.047, 1.068	<0.001	1.052	1.041, 1.064	<0.001
eGFR, ml/min	0.980	0.974, 0.987	<0.001	0.987	0.976, 0.999	<0.029
			Deaths due to other causes			
Sex (male)	2.186	1.452, 3.289	<0.001	2.529	1.471, 4.346	<0.001
Age, years	1.075	1.057, 1.094	<0.001	1.029	1.009, 1.037	0.018
sPAP, mmHg	1.038	1.026, 1.051	<0.001	1.023	1.009, 1.037	<0.001
eGFR, ml/min	0.976	0.970, 0.983	<0.001	0.984	0.973, 0.995	<0.001

sPAP, systolic pulmonary arterial pressure; eGFR: estimated glomerular filtration rate.

by sPAP (HR = 1.052, 95% CI: 1.040, 1.064; *P* < 0.001) and eGFR (HR = 0.987, 95% CI: 0.976, 0.999; *P* < 0.05). In both univariable and multivariable analysis, age, sex, sPAP and eGFR were significantly predictive for cumulative incidence of deaths due to others causes (Table 2).

OS analysis in SRC patients

Of all the SSc patients, 53 (1.5%) were identified as having SRC. Fourteen of the SSc patients with SRC (26.4%) died during follow-up (OS at 5 years 0.655, 95% CI: 0.518, 0.830). The median (IQR) value of eGFR at SRC onset was 36.5 (23.16–49.85) ml/min. The median

(IQR) value of eGFR [33.7 ml/min (19.14–50.48)] at last follow-up did not show significant differences (*P* > 0.05) from the baseline eGFR for patients with SRC. The OS at 5 years of the 53 SRC patients with SRC did not differ significantly between those with eGFR >30 ml/min and those with eGFR ≤30 ml/min (Fig. 4).

Discussion

In this large cohort of SSc patients from the EUSTAR registry, the eGFR was normal or only slightly reduced.

Fig. 4 Overall survival in 53 SSc patients with scleroderma renal crisis according to the estimated glomerular filtration rate (eGFR). The overall survival is not significantly different in SSc patients with eGFR ≤30 ml/min (continuous line) than in SSc patients with eGFR > 30 ml/min (dotted line)
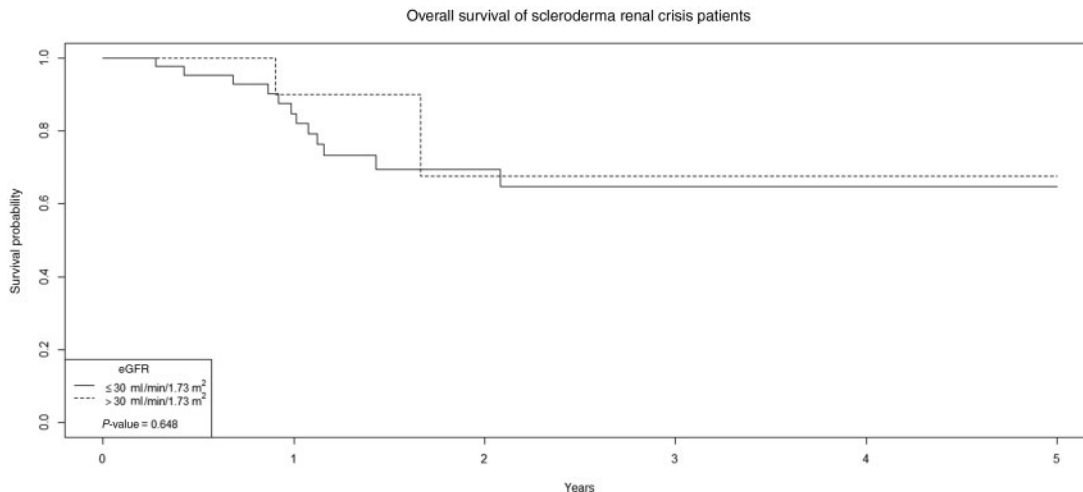
The eGFR was higher in SSc patients with PH. In SSc patients, eGFR represented a predictive risk factor for mortality due to SSc and other causes. The eGFR did not represent a predictive risk factor for mortality in those SSc patients with SRC.

To date, kidney damage in SSc patients has mostly been studied in patients with SRC [11–13]. Only a few, small and monocentric studies have evaluated GFR in other SSc patients. In 26 SSc patients, Kingdon et al. [14] estimated GFR by Equation (7) from the Modification of Diet in Renal Disease (MDRD), and they recommend the use of the MDRD equation for estimating GFR. In 41 SSc patients, Gigante et al. measured GFR using technetium-99 m diethylene-triamine-pentaacetate, and they correlate it with GFR estimated with both MDRD and CKD-EPI equations. Gigante et al. recommend the use of the CKD-EPI equation for estimating GFR in SSc patients with normal serum creatinine [15]. No studies have been previously conducted to evaluate eGFR as a predictive risk factor for mortality due to SSc and other causes in SSc patients.

In our study, serum creatinine was in the normal range and eGFR was slightly reduced in SSc patients. The mean value of eGFR in our population was classified in CKD stage 2. In SSc patients with reduced eGFR, the serum creatinine value was reported as in the normal range due to reduced mass muscle [16]. Subclinical renal involvement, characterized by slight reduction of kidney function, has previously been associated with a favourable outcome [17]. Asymptomatic renal functional impairment affects 10–55% of SSc patients. Although asymptomatic renal changes are typically non- progressive in SSc, some investigators have suggested that they indicate reduced renal functional reserve [18]. In SSc, subclinical kidney involvement is related to vascular injury and chronic hypoxia that can modify renal morphology [19]. Serum creatinine is a poor marker of renal damage, and several formulae have been used to better estimate GFR. In the past, the 7-variable MDRD was the best formula for assessing renal function in SSc patients [14]. Subsequently, the greatest correlation between measured GFR and eGFR in SSc patients was obtained using the CKD-EPI equation [16]. It is well known that the CKD-EPI is more accurate than MDRD at higher GFRs [9], and in SSc the decrease in GFR is generally mild and does not seem to be progressive [17].

In this study, eGFR was reduced in SSc patients with PH. Several studies have reported that GFR reduction is associated with vascular manifestations and poor prognosis [17, 20, 21]. In SSc-associated PH, eGFR is a strong predictor of survival, and renal impairment contributes to increased mortality [22]. In the course of PH, the increase in right atrial pressures leads to renal venous congestion with alterations of haemodynamic parameters that promote GFR reduction [23]. In this study, univariable analysis demonstrated that male gender, age, increased sPAP and reduced eGFR were negative predictive factors for OS at the 5-year follow-up. In multivariable analysis, only increased sPAP and reduced eGFR represented negative predictors of survival. Thus, our results support the hypothesis that sPAP and eGFR represent risk factors for SSc death. In the EUSTAR population, it has been reported that an sPAP >36 mmHg at baseline is significantly and independently associated with reduced survival, regardless of the presence of PH based on right heart catheterization [23, 24]. No studies have been reported on the eGFR as a predictor of mortality in SSc patients, although kidney disease has a major effect, as a direct cause of global morbidity and mortality and as an important risk factor for cardiovascular disease [25].

We demonstrated that mortality due to SSc is higher in SSc patients with eGFR < 60 ml/min and that mortality due to SSc was higher in patients with stages 3–5 CKD than in patients with stages 1 and 2 CKD. In univariable analysis, mortality due to SSc was associated with age, male sex, sPAP and eGFR. In multivariable analysis, mortality due to SSc was predictive from baseline sPAP and GFR. These results indicate that increased sPAP and reduced eGFR represented predictive risk factors for death due to SSc. In a previous study, the authors combined two complementary and detailed databases (3700 deaths) and demonstrated that cardiopulmonary complications were major causes of SSc mortality. Progressive skin fibrosis within 1 year is associated with decline in lung function and worse survival in dcSSc [26]. Although it has been noted that cardiopulmonary involvement and skin fibrosis are predictive risk factors of mortality in SSc patients, no studies have yet reported that reduced kidney function also represents a predictive risk factor for mortality due to SSc.

SSc patients with reduction of the eGFR below 60 ml/min, and especially those with stages 3–5 CKD, should be considered at greater risk of death due to all causes. The sensitivity of the eGFR as a risk factor for all-cause mortality increases in patients with eGFR < 60 ml/min and stages 3–5 CKD. In the univariable and multivariable analysis, all-cause mortality significantly depended on age, male sex, sPAP and eGFR. In SSc patients, all-cause mortality was related to both known demographic variables (age and male gender) and disease variables (sPAP and eGFR).

In the 53 SSc patients with SRC, we showed that an eGFR < 30 ml/min did not represent a predictive risk factors for all-cause mortality. We chose a cut-off of 30 ml/min, because all patients with SRC had an eGFR < 60 ml/min. In the Spanish Network for SSc Registry, older age at disease onset, dcSSc, interstitial lung disease, PH and SRC were all independent risk factors for mortality [27]. SRC is a rare and potentially life-threatening complication that affects 3% of patients with lcSSc and 11% of patients with dcSSc [28]. Current patient survival is estimated at 70–82% at 1 year but decreases to 50–60% at 5 years, despite renal replacement therapy support. In a recent study of SSc patients within 4 years of onset of non-RP symptoms, SRC-related mortality was ~14% [28]. The occurrence of SRC is an independent predictor of 3-year mortality in patients with SSc, as shown for the EUSTAR database [24]. The factors associated with a poor outcome are older age, male sex, congestive heart failure, poorly controlled blood pressure, exposure to glucocorticoids, elevated serum creatinine level at presentation, normotensive SRC, and use of angiotensin-converting enzyme inhibitors prior to the onset of SRC. Patients with SRC who show no signs of renal functional recovery despite timely blood pressure control are candidates for transplantation [29]. Although SRC represents one of the most important causes of mortality among SSc patients, we demonstrate that eGFR is not a mortality risk factor among patients with SRC.

This study has some limitations. We do not know whether renal dysfunction or SRC were the causes of deaths. In the EUSTAR database, only the date of death and whether it was due to SSc were registered—the specific causes are unknown. In particular, there are no data in the EUSTAR database on cardiovascular disease and mortality. This is an important limitation of this study. Although we know the number of SSc patients with arterial hypertension, from the EUSTAR database we cannot retrieve blood pressure values, complications related to arterial hypertension (e.g. hypertensive nephropathy) or medication. This is another important limitation of the study, because we cannot exclude whether arterial hypertension was the cause of reduction of eGFR and mortality from cardiovascular complications. The absence of data on albuminuria and proteinuria in the EUSTAR database represents a third important limitation, not only with respect to correctly defining the CKD stages, but also to precisely defining SRC. In addition, the eGFR value was not directly entered by the centres, but was estimated by the authors, using the EUSTAR database data at the time of the visit of enrolment.

The eGFR is a simple non-invasive tool for early detection of renal function, and its association with other clinical features can be used for risk assessment. Worldwide, patients with eGFR reduction develop a higher risk of poor outcomes.

Taken together, it can be concluded that the mean value of eGFR is normal or slightly reduced in SSc patients, and lower values of eGFR are associated with PH. eGFR represents a predictive risk factor for mortality due to SSc or other causes in the overall SSc cohort, but it does not represent a risk factor for mortality among those SSc patients with SRC.

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Data availability statement

The authors confirm that all data are presented in the main manuscript.

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