

Why Men Fare Worse: Understanding Gender Disparities in Systemic Sclerosis-Associated Pulmonary Hypertension

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Abstract

Objective: This study investigates gender disparities in clinical outcomes among patients with systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH), focusing on cardiovascular events, right ventricular function, and survival.

Introduction: PAH is a severe and life-threatening complication of SSc, with male patients often experiencing worse outcomes despite its higher prevalence in women. Comparative data on gender differences in this population remain limited.

Methods: We conducted a retrospective, single-center study including 61 patients with SSc-associated PAH (52 women, 9 men), confirmed by right heart catheterization. Clinical, serological, pulmonary, and echocardiographic data were analyzed. Differences between sexes in cardiovascular events, right ventricular dilation, and survival were evaluated using appropriate statistical methods.

Results: Male patients had a significantly higher incidence of cardiovascular events (median: 2.00 vs 1.00 in women; $P=.031$) and a greater prevalence of right ventricular dilation (100.00% vs 44.23%; $P=.002$). Kaplan-Meier analysis demonstrated reduced cardiovascular event-free survival ($P=.001$) and overall survival ($P=.014$) in men. Although mortality was higher in men (88.89%) than in women (57.69%), the difference was not statistically significant ($P=.134$).

Conclusion: Men with SSc-associated PAH experience worse clinical outcomes, including more frequent cardiovascular events and reduced survival. The absence of estrogen's protective effects and the adverse influence of testosterone on cardiac remodeling may contribute to these disparities. These findings highlight the importance of early gender-specific risk stratification and the need for tailored therapeutic strategies to improve outcomes in this high-risk group.

Keywords

scleroderma-associated pulmonary arterial hypertension (PAH), right ventricular dilation, cardiovascular events, gender disparities

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Introduction

Systemic sclerosis (SSc), or scleroderma, is a complex autoimmune disease characterized by fibrosis, vascular alterations, and a wide clinical variability, often leading to severe complications such as pulmonary hypertension (PH). The development of PH in patients with SSc significantly increases the risk of mortality and is associated with worse survival compared to other forms of PH.¹

Previous research on large cohorts of patients has underscored the critical role of pulmonary complications, including PH, in determining prognosis and survival.²

Although systemic sclerosis predominantly affects women, with a female-to-male ratio ranging from 4:1 to 6:1, male patients often experience more aggressive disease forms and a higher rate of severe cardiovascular and pulmonary complications.³ Among these complications, pulmonary arterial hypertension (PAH) stands out as particularly severe, significantly worsening patient outcomes. While PAH remains more prevalent among women, men diagnosed with PAH associated with systemic sclerosis have consistently poorer prognoses, including increased cardiovascular events and higher mortality rates.⁴⁻⁶

Capillaroscopic patterns, particularly nailfold capillary loss and advanced capillary abnormalities, have been identified as important markers predictive of PAH development specifically in patient with SSc, highlighting the role of early diagnostic strategies.⁷ Moreover, right ventricular dysfunction, recognized as a critical prognostic factor in systemic sclerosis-associated PAH, could represent a key mechanism behind gender disparities in disease progression and outcomes.⁸⁻¹⁰

Lifestyle factors, such as physical activity, also play a significant role in disease outcomes and management. Regular exercise has shown beneficial effects on cardiovascular health in various chronic conditions, suggesting potential advantages for patients with systemic sclerosis and associated PAH.¹¹⁻¹⁴

From a pathophysiological perspective, PAH in SSc arises from a combination of endothelial dysfunction, vascular remodeling, inflammation, and fibrosis. Vascular injury leads to intimal proliferation, medial hypertrophy, and perivascular inflammation, ultimately increasing pulmonary vascular resistance. This increased afterload progressively impairs right ventricular function, contributing to right heart failure. Notably, hormonal factors also modulate these pathways: estrogens exhibit vasodilatory and anti-fibrotic properties, while testosterone may promote adverse remodeling, potentially explaining the worse outcomes observed in males.¹⁵⁻¹⁸

Additionally, the progression and severity of systemic sclerosis differ significantly between genders, influenced by complex interactions among hormonal, genetic, and physiological factors. Specifically, estrogen may exert protective cardiovascular and anti-fibrotic effects, whereas testosterone appears to have a detrimental influence on cardiac remodeling in male patients, contributing to their worse prognosis.^{19,20}

Besides biological factors, lifestyle and behavioral elements such as physical activity, sedentary behavior, and dietary habits significantly impact disease progression and management, underscoring the importance of a holistic approach to patient care and risk factor modification.²¹⁻²³ Furthermore, gender-related genetic differences in inflammation and vascular remodeling responses could further explain these disparities.

Given these premises, the aim of the present study is to delineate and compare the clinical profiles of male and female patients affected by systemic sclerosis-associated PAH, focusing particularly on male patients, who typically have worse clinical outcomes. Early identification of these gender-specific clinical characteristics may inform more targeted therapeutic strategies, ultimately improving prognosis and quality of life.

Patients and Methods

Study Design

This retrospective single-center study analyzed 61 individuals, comprising 52 women (85.25%) and 9 men (14.75%), with an average age of 73.0 years. The women had a mean age of 72.2 years, while the men had a mean age of 77.3 years. All participants were affected by SSc, as defined by the 2013 ACR/EULAR classification criteria. They were referred to the Scleroderma Unit of AOU Policlinic of Modena and underwent right heart catheterization (RHC) at the Cardiology Unit of Policlinic of Modena between October 2013 and October 2023. The RHC findings confirmed the presence of pulmonary hypertension, with measurements meeting the criteria outlined in the latest 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.¹⁷

The primary aim was to compare the clinical characteristics of male and female patients with SSc with pulmonary hypertension to identify distinguishing features. We also analyzed a comparable group of 70 individuals, consisting of 61 women (87.14%) and 9 men (12.86%), with a mean age of 62.87 years, all affected by SSc with a low risk of developing pulmonary hypertension according to the 2021 ESC guidelines, in order to exclude that such characteristics were solely attributable to SSc. The study was approved by the local ethics committee Area Vasta Emilia Nord (protocol no 275/16) and conducted in accordance with the Good Clinical Practice Guidelines and the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh. Written informed consent was obtained from all subjects prior to study initiation. In addition, written informed consent was obtained from all participants for the publication of this study.

Parameters Assessed

All patients with SSc included in this study underwent a thorough evaluation encompassing clinical, serological, and instrumental assessments within 12 months prior to RHC.

Table 1. Demographic and Anthropometric Characteristics of Patients With SSc, Comparing the PH Group and the Control Group Without PH.

Parameter	PH Group (n = 61)	Control group no PH (n = 70)
Women (%)	85.25% (n = 52)	87.14% (n = 61)
Men (%)	14.75% (n = 9)	12.86% (n = 9)
Age (y)	73.38 ± 9.43	63.10 ± 12.03
Height (cm)	164.99 ± 6.03	169.99 ± 7.29
Weight (kg)	65.85 ± 10.63	71.75 ± 8.63
BMI (kg/m ²)	24.29 ± 4.26	27.26 ± 3.69

Abbreviations: PH, pulmonary hypertension; SSc, systemic sclerosis.

The medical history and physical examination were detailed, focusing on the classification of cutaneous subsets according to Leroy et al, the modified Rodnan skin score (mRSS), and the presence of digital ulcers or pitting scars.

Functional capacity was assessed using the New York Heart Association (NYHA) classification, while information on mortality and cardiovascular events was meticulously recorded. Cardiovascular events were defined as the composite of clinically documented heart failure (both right and left), ischemic events (such as myocardial infarction or angina requiring intervention), sustained arrhythmias requiring therapy (eg, atrial fibrillation or ventricular tachycardia), and sudden cardiac death. These were identified through clinical records, hospitalization data, or cardiologic follow-up documentation.

Additionally, the use of PAH-specific therapies during follow-up after RHC was documented.

The autoimmune serological profile was analyzed for the presence of systemic sclerosis-specific antibodies, including anti-centromere antibodies (ACA), anti-topoisomerase I antibodies (Scl70/ATA), and anti-RNA polymerase III (RPIII), alongside non-SSc-specific autoantibodies.

To further explore disease activity, nailfold videocapillaroscopy (NVC) was performed to identify SSc patterns classified as early, active, or late stages.

Pulmonary function tests (PFTs) were conducted to measure vital parameters such as transfer factor of the lung for carbon monoxide (TLCO), forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), and exercise capacity through the 6-minute walk test (6MWT).

High-resolution computed tomography (HRCT) was employed to evaluate the presence and extent of interstitial lung disease (ILD), with severity quantified according to the Goh visual staging system.

Cardiac function was evaluated using echocardiography performed by an experienced researcher. This included assessments of ventricular dimensions, left ventricular ejection fraction, tricuspid annular plane systolic excursion (TAPSE), and right atrium area. The researcher performing the echocardiographic analysis was blinded to the patients' clinical data and group assignment. Pulmonary arterial systolic pressures (PAPs) were determined from the peak

tricuspid jet velocity, using the simplified Bernoulli equation combined with an estimate of right atrial pressure.

Finally, RHC was carried out following standard procedures to confirm the presence of pulmonary hypertension. Key hemodynamic parameters, including mean pulmonary arterial pressure (PAPm), wedge pressure, and pulmonary vascular resistance (PVR), were measured. Pulmonary hypertension was diagnosed and classified according to the 2022 ESC/ERS guidelines, and patients with extensive ILD were categorized as PH Group 3.

Statistical Analysis

Statistical analyses were conducted using SPSS software (IBM) and Prism GraphPad (version 8.1). Continuous variables were tested for normality using the Shapiro-Wilk test. Non-normally distributed variables or small sample sizes were analyzed with non-parametric tests such as the Mann-Whitney *U* test, while normally distributed variables were assessed using Student's *t*-test. Categorical data were expressed as frequencies and compared using chi-square or Fisher's exact test, depending on the sample size. Kaplan-Meier curves were employed to represent survival and cardiovascular events, with statistical comparisons made using the log-rank test. A *P* value lower than .05 was considered significant.

Results

We enrolled and analyzed 61 systemic sclerosis (SSc) patients with pulmonary hypertension (PH), including 52 women (85.25%) and 9 men (14.75%), with a mean age at enrolment of 73.38 ± 9.43 years, reflecting the typical gender distribution observed in SSc patients. For comparison, we also enrolled 70 SSc patients without PH, consisting of 61 women (87.14%) and 9 men (12.86%), with a mean age of 63.10 ± 12.03 years. Demographic and anthropometric data, summarized in Table 1, confirmed that the 2 cohorts were comparable regarding gender distribution, age, and anthropometric measures, that supporting valid clinical outcome comparisons between the groups.

Men were found to have a significantly higher number of cardiovascular events compared to women (Median: 2.00 in men vs 1.00 in women; *P* = .031; Table 2). Additionally, men had a significantly higher prevalence of right ventricular dilation (100.00% in men vs 44.23% in women; *P* = .002; Table 2). Kaplan-Meier analysis revealed a reduction in cardiovascular event-free survival in men compared with women (log-rank χ^2 = 10.664; *P* = .001; Figure 1A). In addition, men showed a significantly lower overall survival than women (log-rank χ^2 = 5.986; *P* = .014; Figure 1B). While mortality was higher in men compared to women (88.89% vs 57.69%), this difference was not statistically significant (*P* = .134). Similarly, other variables such as pericardial effusion (33.33% in men vs 11.54% in women; *P* = .124), renal crises (11.11% in men vs 1.92% in women; *P* = .275), and anti-RNA polymerase III positivity (11.11% in men vs 0.00% in women; *P* = .148), prevalence

Table 2. Clinical and Instrumental Characteristics of SSs Patients With and Without PH, Stratified by Gender.

Variable (patient with PH)	Male (n = 9), median (confidence interval)	Female (n = 52), median (confidence interval)	P value	Variable (patients without PH)	Male (N = 9), median (confidence interval)	Female (n = 61), median (confidence interval)	P value
NYHA-stage	3.00 (2.50-3.50)	3.00 (2.50-3.50)	.896	NYHA-Stage	1.00 (0.32-1.68)	2.00 (1.74-2.26)	.487
Modified Rodnan skin score	8.00 (7.00-9.00)	6.00 (5.00-7.00)	.523	Modified Rodnan skin score	6.00 (4.50-7.50)	4.00 (3.00-5.00)	.778
Left ventricular ejection fraction (%)	55.00 (52.00-58.00)	55.00 (52.00-58.00)	.256	Left ventricular ejection fraction (%)	60.00 (56.00-64.00)	59.00 (57.00-62.00)	.187
TRV (m/s)	3.10 (2.95-3.25)	3.45 (3.30-3.60)	.021	TRV (m/s)	2.10 (1.85-2.35)	2.35 (2.24-2.46)	.273
TAPSE (mm)	20.00 (19.00-21.00)	20.00 (19.00-21.00)	.505	TAPSE (mm)	23.00 (20.00-24.00)	22.00 (20.00-21.00)	.505
PAPs (mmHg) on ECHO	45.00 (42.00-48.00)	55.00 (52.00-58.00)	.078	PAPs (mmHg) on ECHO	23.00 (19.37-26.63)	27.50 (25.94-29.06)	.140
TAPSE/PAPs	0.48 (0.45-0.51)	0.37 (0.34-0.40)	.440	TAPSE/PAPs	0.93 (0.80-1.06)	0.87 (0.78-0.96)	.486
PAP mean (mmHg) on RHC	33.00 (31.00-35.00)	33.00 (31.00-35.00)	.335	—	—	—	—
PVR (WU)	4.42 (4.20-4.64)	4.70 (4.48-4.92)	.512	—	—	—	—
Wedge pressure (mmHg)	12.00 (11.00-13.00)	11.50 (10.50-12.50)	.420	—	—	—	—
6MWT (distance in m)	420.00 (400.00-440.00)	400.00 (380.00-420.00)	.418	6MWT (distance in m)	510.00 (440.00-550.00)	460.00 (400.00-500.00)	.118
DLCO/SB (% predicted)	34.00 (32.00-36.00)	35.00 (33.00-37.00)	.639	DLCO/SB (% predicted)	36.00 (34.00-38.00)	38.00 (35.00-41.00)	.716
DLCO/VA (% predicted)	48.00 (46.00-50.00)	49.50 (47.50-51.50)	.519	DLCO/VA (% predicted)	51.00 (48.00-54.00)	52.50 (49.50-55.50)	.641
FVC (% predicted)	74.00 (71.00-77.00)	86.00 (83.00-89.00)	.113	FVC (% predicted)	76.00 (74.00-78.00)	88.00 (85.00-91.00)	.277
TLC (% predicted)	77.00 (74.00-80.00)	94.50 (91.50-97.50)	.078	TLC (% predicted)	77.00 (74.00-80.00)	94.50 (91.50-97.50)	.078
FVC/DLCO	2.32 (2.25-2.39)	2.58 (2.51-2.65)	.318	FVC/DLCO	2.32 (2.25-2.39)	2.58 (2.51-2.65)	.318
No of CV events	2.00 (1.50-2.50)	1.00 (0.50-1.50)	.031	No of CV events	2.5 (0.0-4.1)	3.3 (0.0-7.8)	.309

Abbreviations: CV, cardiovascular; DLCO/SB, diffusing capacity of the lung for carbon monoxide/single breath; DLCO/VA, diffusing capacity for carbon monoxide corrected by alveolar volume; ECHO, echocardiography; FVC, forced vital capacity; 6MWT, 6-minute walk test; NYHA, New York Heart Association; PAPs, pulmonary artery systolic pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SSs, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion; TLC, total lung capacity; TRV, tricuspid regurgitation velocity. Values are expressed as median with confidence intervals. Statistical significance is indicated by P values (significant P values in bold).

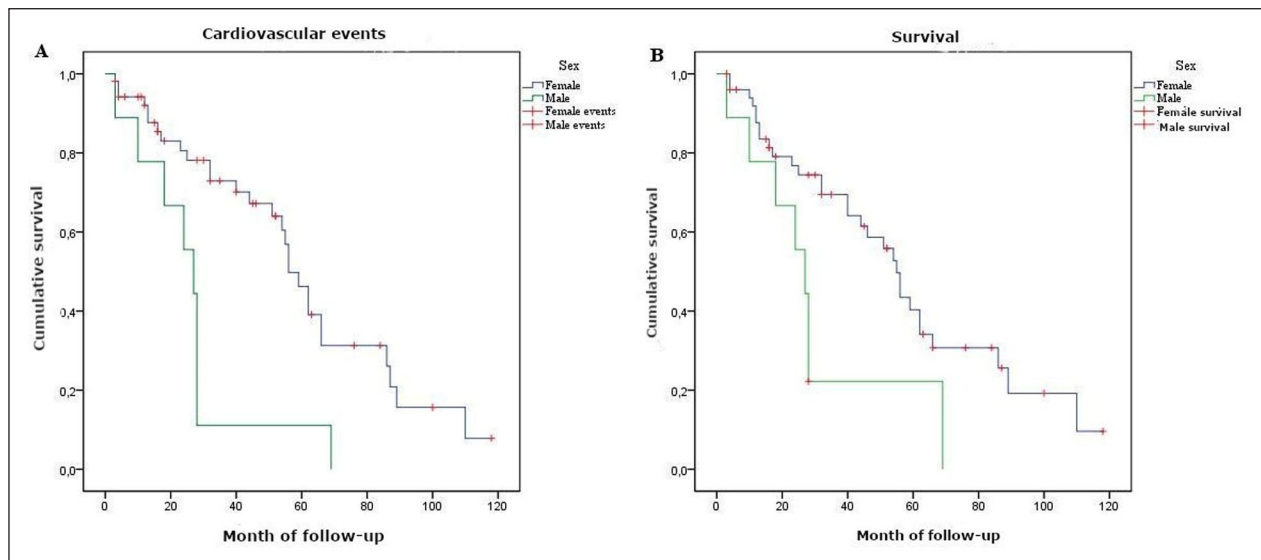


Figure 1. Incidence of cardiovascular events and overall survival in patients with systemic sclerosis-associated pulmonary arterial hypertension, stratified by sex. (A) Kaplan-Meier curves for cardiovascular event-free survival show a significantly higher incidence of events in male patients compared with female patients (log-rank $\chi^2 = 10.664$; $P = .001$). (B) Kaplan-Meier curves for overall survival demonstrate a significantly lower survival in male patients than in female patients (log-rank $\chi^2 = 5.986$; $P = .014$). Plus signs (+) indicate the time at which a cardiovascular event (A) or death (B) occurred.

of active disease patterns (66.67% in men vs 36.54% in women; $P = .142$) and extensive interstitial lung disease (ILD; 66.67% in men vs 42.31% in women; $P = .278$), were not different between men and women.

To validate that these findings were driven by PH rather than SSc per se, we analyzed a control group of SSc patients without PH matched for age and gender. In this control group, there were no significant differences in the assessed parameters, except for a tendency toward telangiectasia in women, confirming that the distinctive profiles are specific to SSc-associated PH (Tables 2 and 3).

Discussion

In our study, we identified significant gender disparities among patients with systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH). Men exhibited a significantly higher prevalence of right ventricular dilation compared to women (100.00% vs 44.23%; $P = .002$), reflecting considerable cardiac impairment in this group. This finding aligns with previous studies reporting right ventricular dilation as a critical negative prognostic factor in male SSc patients.²⁴

Additionally, male patients experienced a significantly higher median number of cardiovascular events compared to women (median: 2.00 in men vs 1.00 in women; $P = .031$), underscoring increased cardiovascular vulnerability among males.²⁵

Kaplan-Meier curves further confirmed significantly reduced cardiovascular event-free survival in men (log-rank $\chi^2 = 10.664$, $P = .001$). Hormonal factors, particularly testosterone, may influence these results by negatively affecting cardiac remodeling, thereby exacerbating susceptibility to severe cardiovascular complications.²⁴

Overall survival was also significantly lower in men, as illustrated by Kaplan-Meier survival curves (log-rank $\chi^2 = 5.986$, $P = .014$), despite absolute differences in mortality rates (88.89% men vs 57.69% women; $P = .134$) not reaching statistical significance. This aligns with existing literature indicating generally poorer outcomes in male patients with SSc-PAH, emphasizing the importance of early cardiac assessment and targeted intervention strategies.²⁶

Contrary to other studies, our group did not identify statistically significant differences regarding the prevalence of pericardial effusion, renal crises, anti-RNA polymerase III positivity, capillaroscopic activity patterns, or extensive ILD. This discrepancy highlights variability in clinical manifestations and underscores the need for further studies with larger cohorts to clarify potential gender-related differences.²⁷⁻³²

The absence of protective estrogen effects in men may partially explain the higher prevalence of right ventricular dilation, cardiovascular events, and pulmonary involvement, particularly pulmonary fibrosis, observed in this population. Estrogens indeed exert protective vascular, cardiac, and anti-fibrotic properties, potentially contributing to better clinical outcomes observed in women.^{24,29} Hormonal modulation therapies and structured, personalized cardiovascular rehabilitation programs might significantly benefit male patients, enhancing both clinical outcomes and quality of life.^{33,34}

Future prospective studies with larger cohorts and comprehensive longitudinal assessments are essential to confirm our findings and further elucidate the biological mechanisms underpinning gender disparities in SSc-associated PAH, thus optimizing the development of targeted therapeutic interventions.

Table 3. Clinical and Serological Features of SSc Patients With and Without PH, Stratified by Gender..

Variable (patients with PH)	Male (n = 9), percentage (confidence interval)	Female (n = 52), median (confidence interval)	P value	Variable (patients without PH)	Male (n = 9), percentage (confidence interval)	Female (N = 61), percentage (confidence interval)	P value
Right ventricular dilation	100.00% (66.37-100.00)	44.23% (30.24-59.30)	.002	Right ventricular dilation	0 (0.0)	0 (0.0)	1.000
Telangiectasia	33.33% (11.82-64.55)	80.77% (67.57-89.53)	.007	Telangiectasia	44.4 (11.9-76.9)	70.0 (58.4-81.6)	.148
ACA positivity	11.11% (1.98-42.94)	51.92% (38.12-65.47)	.031	ACA positivity	16.13% (7.38-39.21)	43.98% (27.65-56.32)	.088
Pericardial effusion	33.33% (11.82-64.55)	11.54% (5.44-23.00)	.124	Pericardial effusion	0.0 (0.0-0.0)	5.0 (0.0-10.5)	1.000
Death	88.89% (55.22-98.25)	57.69% (43.28-71.02)	.134	Death	0 (0.0-0.0)	1.6 (0.0-4.8)	1.000
Active pattern	66.67% (35.45-88.18)	36.54% (24.71-50.12)	.141	Active pattern	29 (0.0-73.7)	35 (22.5-47.4)	1.000
Anti-RNA Pol III Ab positivity	11.11% (1.98-42.94)	0.00% (0.00-7.31)	.147	Anti-RNA Pol III Ab positivity	11.1 (0.0-31.6)	5.0 (0.0-10.5)	.436
Late pattern	22.22% (6.23-52.76)	51.92% (38.12-65.47)	.151	Late pattern	18.30% (3.48-45.79)	44.23% (31.25-56)	.257
TAPSE/PAPs ≤0.6	77.78% (47.24-93.77)	92.31% (81.20-97.06)	.212	TAPSE/PAPs ≤0.6	0%	0%	1
Limited ILD	11.11% (1.98-42.94)	34.62% (23.06-48.39)	.250	Limited ILD	7.97% (0.5-36)	21.98% (9.78-37.25)	.360
Renal crisis	11.11% (1.98-42.94)	1.92% (0.34-10.27)	.275	Renal crisis	0 (0.0-0.0)	1.6 (0.0-4.84)	1.000
Extensive ILD	66.67% (35.45-88.18)	42.31% (29.88-55.85)	.278	Extensive ILD	50 (5.31-94.7)	45 (32.4-57.9)	1.000
TAPSE/PAPs ≤0.19	11.11% (1.98-42.94)	5.77% (2.18-14.37)	.481	TAPSE/PAPs ≤0.19	0%	0%	1.000
Cigarette smoking ever	55.56% (26.91-81.24)	42.31% (29.88-55.85)	.491	Cigarette smoking ever	61.12% (51.31-72.62)	43.88% (31.6-57.8)	.537
Anti Scl-70 Ab positivity	33.33% (11.82-64.55)	26.92% (16.76-40.12)	.699	Anti Scl-70 Ab positivity	22.22% (6.23-52.76)	21.31% (12.28-33.10)	.940
ILD/COPD on HRCT	77.78% (47.24-93.77)	76.92% (62.48-87.02)	1.000	ILD/COPD on HRCT	22.22% (6.23-52.76)	29.51% (19.28-42.10)	.810
Digital ulcers (ever)	55.56% (26.91-81.24)	55.77% (41.49-69.08)	1.000	Digital ulcers (ever)	55.61% (23.1-88.0)	50.09% (37.3-62.7)	1.000
TAPSE/PAPs ≤0.32	33.33% (11.82-64.55)	38.46% (25.91-52.93)	1.000	TAPSE/PAPs ≤0.32	0%	0%	1.000
ANA positivity	100.00% (66.37-100.00)	96.15% (85.78-99.06)	1.000	ANA positivity	88.89% (55.22-98.25)	93.44% (84.25-97.44)	.601

Abbreviations: ACA, anti-centromere antibodies; ANA, anti-nuclear antibodies; COPD, chronic obstructive pulmonary disease; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; PAPs, pulmonary artery systolic pressure; PH, pulmonary hypertension; Pol III Ab, polymerase III antibodies; SSc, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion. Values are expressed as percentages with 95% confidence intervals. Statistically significant differences are highlighted by bold P values.

Limitations of the Study

This study has several limitations that should be considered when interpreting the results.

First, the sample size, particularly of male patients (9 men compared to 52 women), is relatively small, which may limit the generalizability of our findings. The known gender disparity in the prevalence of scleroderma-associated pulmonary hypertension (PAH) contributes to this imbalance, but future studies with larger, multicenter cohorts are needed to validate these results.

No *a priori* sample size calculation was performed, as this was a retrospective study including all eligible patients within a defined 10-year time frame.

Second, the retrospective design of the study may introduce inherent biases related to data collection and analysis. Retrospective data lack the precision of prospectively collected information, and there is a potential for missing or incomplete data, particularly in the long-term follow-up of these patients.

Third, while our comparison group included systemic sclerosis (SSc) patients without PAH, the exclusion of PAH was based on echocardiographic parameters according to the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines. Although this method is standard, it does not entirely eliminate the risk of undiagnosed cases of early or subclinical PAH, potentially introducing a selection bias.

Fourth, while several findings did not reach statistical significance, their potential clinical relevance cannot be dismissed. For instance, the observed differences in mortality, pericardial effusion, and ILD prevalence between men and women highlight trends that may have important implications for disease management. These results should be interpreted cautiously, acknowledging the limitations of sample size and statistical power.

Finally, the study did not include a detailed longitudinal analysis, limiting the ability to fully assess the long-term impact of gender-specific factors on disease progression and outcomes. Prospective studies with extended follow-up would be beneficial to better understand the progression of PAH in male versus female patients and to assess the potential benefits of targeted interventions.

Conclusions

This study highlights significant gender disparities in SSc-associated PAH, with male patients experiencing more severe cardiovascular outcomes and reduced survival compared to female patients. Men exhibited a higher prevalence of right ventricular dilation and a greater number of cardiovascular events, underscoring the increased cardiac vulnerability in this group. Although the overall mortality difference between men and women was not statistically significant, Kaplan-Meier survival curves demonstrated a clear trend toward lower survival in men, warranting further clinical attention.

The absence of the protective effects of estrogen and the detrimental influence of testosterone on cardiac remodeling are likely contributing factors to these gender-specific differences. These results underscore the critical importance of

adopting gender-specific management approaches in clinical practice. Early, routine cardiovascular assessments, targeted hormonal modulation therapies, and personalized rehabilitation programs may substantially improve outcomes for male patients.

Future research should focus on understanding the biological mechanisms behind gender disparities in SSc-associated PAH, facilitating the development of tailored therapeutic strategies and ultimately enhancing prognosis and quality of life for this high-risk patient group.

List of Abbreviations

PAH:	Pulmonary arterial hypertension
SSc:	Systemic sclerosis
RHC:	Right heart catheterization
NYHA:	New York Heart Association
ILD:	Interstitial lung disease
ACA:	Anti-centromere antibodies
ScI70:	Anti-topoisomerase I antibodies
RPIII:	Anti-RNA polymerase III antibodies
mRSS:	Modified Rodnan skin score
NVC:	Nailfold videocapillaroscopy
PFTs:	Pulmonary function tests
HRCT:	High-resolution computed tomography
PAPs:	Pulmonary artery pressures
TAPSE:	Tricuspid annular plane systolic excursion
PVR:	Pulmonary vascular resistance
TLCO:	Transfer factor of the lung for carbon monoxide
FVC:	Forced vital capacity
DLCO:	Diffusing capacity of the lung for carbon monoxide
6MWT:	6-Minute walk test
ESC/ERS:	European Society of Cardiology/European Respiratory Society

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FC and GP contributed equally to study design, data analysis, and manuscript drafting. AN, MdP, and AS contributed to data collection and interpretation. SC and VS contributed to pulmonary and immunological data evaluation. DA, AVM, GB, FF, and DG provided critical revision, cardiological and rheumatological expertise, supervision of the project, and contributed to patient recruitment. MP contributed to the pathophysiological interpretation and overall coordination. All authors read and approved the final version of the manuscript.

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Declaration of Conflicting Interests

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