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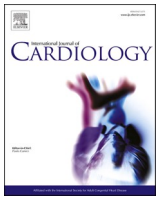

Pulmonary hypertension in patients with Sjögren's syndrome: Gender differences in cardiovascular risk factors and instrumental data

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ABSTRACT

Background: Pulmonary hypertension (pH) is a well-documented complication in patients with connective tissue diseases, including Sjögren's syndrome (SS). However, the prevalence of PH in SS varies considerably across studies, likely due to differences in diagnostic methods.
Aim of the study: This study aims to assess the prevalence of PH in a cohort of SS patients and to examine potential differences in age, cardiovascular risk factors, autoimmunity, pulmonary function tests, and echocardiographic parameters between male and female SS patients.
Patients and methods: Sixty-three patients diagnosed with primary SS were included in this study. Male patients were compared to females regarding age, cardiovascular risk factors, autoimmunity, pulmonary function tests, and echocardiographic parameters. All patients underwent comprehensive cardiac echo-color-Doppler evaluations during their most recent follow-up.
Results: The prevalence of PH in the study cohort was 1.6 %. Respiratory function tests revealed significantly lower values in male patients compared to females. Echocardiographic assessments also indicated more pronounced alterations in males in pulmonary artery diameter and TVI-RVOT. In left-sided heart parameters, males showed greater dilatation and signs of diastolic dysfunction. Mass 2D and ejection fraction FE2D were also altered in males.
Discussion and conclusion: The low prevalence of PH (1.6 %) in SS patients when diagnosed with RHC emphasizes the importance of using accurate diagnostic methods. As male patients demonstrated a greater predisposition to developing PH, as evidenced by altered respiratory function, and early diastolic dysfunction, regular echocardiographic monitoring is recommended for male SS patients, particularly those exhibiting early structural or functional cardiac changes.

1. Introduction

Sjögren's syndrome (SS) is a chronic systemic autoimmune inflammatory disease characterized by focal lymphocytic infiltration of the exocrine glands, mainly affecting the salivary and lacrimal glands [1,2]. Clinically, 80 % of cases cause severe dryness of mucosal surfaces, especially of the mouth and eyes, but may also extend to the skin, nose, pharynx, and vagina. Extra-glandular pathologic manifestations affecting organs and apparatuses may also occur, giving skin, renal, musculoskeletal, hematologic, neurologic, and pulmonary problems. It

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occurs in a primary form not associated with other diseases and in a secondary form that complicates or overlaps with other pathological conditions; the most common diseases associated with SS are rheumatoid arthritis, systemic lupus erythematosus, and scleroderma [3,4]. To date, it has been shown that women are more affected than men, with a 9:1 ratio, and the peak onset of disease is around age 50, in cases where it is diagnosed in younger patients, around age 35, it presents associated with fever and lymphadenopathy [5].

The pathogenesis is considered multifactorial but not completely understood; many of the genes identified so far are involved in interferon, lymphocytic migration, cytokine and receptor function, and other intercellular signaling pathways that are subsets of multiple immune cells [5]. Both T cells and B cells are involved in the pathogenesis of SS with a possible dominant role [6,7].

Sjögren's Syndrome has been identified as an independent risk factor for various cardiovascular complications, including atherosclerosis-induced vascular thickening, myocardial infarction, arrhythmias, and cerebrovascular events such as stroke and transient ischemic attack (TIA) [8]. Other associations include pulmonary hypertension, venous thromboembolism, and hypertriglyceridemia [9]. Although if there is significant evidence of an increased CV risk in patients with SS, the causes and triggers are still not fully understood; currently systemic vasculopathy, B cell activation, and autoimmunity could play an important role in the pathophysiology of the above cardiac disorders [10,11]. SS has been associated with an increased risk of pulmonary hypertension, likely due to chronic inflammation, vascular dysfunction, and immune-mediated endothelial damage, which can contribute to elevated pulmonary arterial pressure and right ventricular strain [8]. In a study on a Greek cohort, pulmonary hypertension has been observed in 20 % of patients with primary SS, and was mild in almost all enrolled patients [12]. Conversely, severe PH has been rarely reported in SS patients [13–15]. PH complicating SS manifests as PAH or Group 3 pH. Sjogren's-PAH is rare, with a reported prevalence of <1 %. [16], while the prevalence of Group 3 pH in the context of SS ILD is not well known. The pathogenetic mechanisms involved in PH associated with SS remain unclear. The development of PH seems to be mediated by two such reciprocally potentiating vascular mechanisms as prolonged vasospasm and structural vessel remodeling, which progressively induce a fixed narrowing of pulmonary arterioles, leading to the thrombotic obstruction which is responsible for the irreversibility of this condition. In this regard, the vasospasm of Raynaud's phenomenon might play an important role in the pathogenesis of PH associated with such connective tissue diseases as SS, preceding, or perhaps, accompanying pulmonary vascular lesions. Pulmonary manifestations of SS affect 9–20 % of patients, with interstitial lung disease (ILD) being the most significant contributor to morbidity and mortality [17]. ILD types include nonspecific interstitial pneumonia, organizational pneumonia, and interstitial pneumonia, commonly presenting with dyspnea and cough. High-resolution computed tomography (HRCT) reveals overlapping patterns with idiopathic interstitial pneumonias. Furthermore, few data exist concerning gender differences in the incidence and features of pulmonary arterial hypertension, despite the strikingly difference in the prevalence of SS between women and men. In this study, we investigated the characteristics and sex differences of the disease in a cohort of 63 patients with SS, in which 24 of them also had ILD, by evaluating 2D and 3D echocardiographic images, electrocardiogram, clinical and hematological data, high-resolution CT (HRTC) and pulmonary functionality.

2. Materials and methods

2.1. Patients

The study was designed as a case-control study. The study protocol received approval from the Ethics Committee Area Vasta Emilia Nord (protocol no. 275/16). Patients included in the study were diagnosed with SS according to the ACR/EULAR classification criteria and were under the care of the Rheumatology Department at the Modena University Hospital [18,19]. As summarized in Table 1, a total of 63 patients were enrolled, comprising 7 males (11.1 %) and 56 females (88.9 %), with a mean age of 69.1 ± 12.5 years (range: 43–90 years). During the follow-up period, three deaths were recorded (4.8 %; 1/7 males and 2/56 females). Smoking status, including both past and current smoking, was also reported. Clinical examinations were conducted at the Cardiology Unit of Modena University Hospital between November 2022 and May 2024. All participants underwent 2D/3D echocardiography and electrocardiography, with right heart catheterization performed when clinically indicated.

2.2. Clinical data and laboratory tests

Data on risk factors, including diabetes, hypertension, dyslipidemia, smoking habits, and the presence of interstitial lung disease, were collected for all patients. Additional information on SS-related characteristics was documented, including immunological profile, symptoms (e.g. dry eyes, dry mouth, Raynaud's phenomenon, and arthralgia), and hematological parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), uric acid, and creatinine. Respiratory function tests were performed to assess forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO), and high-resolution computed tomography (HRCT) of the lungs was used to detect pulmonary fibrosis.

2.3. Cardiovascular assessment

Resting electrocardiograms were conducted for all patients, with results considered positive in the presence of rhythm disturbances (e.g., atrial fibrillation or flutter) or signs of ventricular overload. Furthermore, data on cardiological and rheumatological therapies were systematically collected.

All patients underwent a comprehensive echocardiographic evaluation with color Doppler, in accordance with the latest ASE guidelines [20,21].

This included speckle-tracking analysis to derive right ventricular strain, where feasible. To minimize operator- and machine-dependent variability, all examinations were performed within the final year of follow-up using the same echocardiograph and by the same operator. We systematically assessed the following parameters: Left Ventricular Systolic Function Ejection fraction (EF): 2D and 3D measurements), Right Ventricular Systolic Function (Tricuspid annular plane systolic excursion (TAPSE), 3D ejection fraction of the right ventricle, Right ventricular strain: Free wall and interventricular septal analysis, Tissue Doppler imaging (S′), Fractional area change (FAC)), Left Ventricular Diastolic Function (Trans-mitral flow pattern analysis: Graded as normal (grade 1), delayed relaxation (grade 2), pseudonormal (grade 3), or restrictive (grade 4)), Right Ventricular Dimensions (Basal, mid-cavity, and apico-basal diameters), Right Ventricular Volumetrics (end-

Table 1
Demographic and clinical characteristics of enrolled patients.

	Values	% or range
Females	56/63	88.9 %
Males	7/63	11.1 %
Age (mean ± SD)	69.1 ± 12.5	43–90
Deaths	3/63	4.8 %
Smoking	12/63	19 %
SS duration (years)	9.6 ± 12.5	1–27
Age at diagnosis	59.5 ± 14.4	29–84
ILD	24/63	38.1 %
Weight (kg)	66.4 ± 13.59	44–102
Height (cm)	162.21 ± 7.15	145–179
BMI (kg/m^2)	25.21 ± 4.75	17.3–37.5
BSA (m^2)	1.72 ± 0.19	1.34–2.16

systolic and end-diastolic volumes, assessed in 2D and 3D), Left Ventricular Volumetrics (end-systolic and end-diastolic volumes, calculated using the biplane Simpson method), Left Atrial Volumetrics (end-systolic volume during ventricular systole using the Simpson biplane method), Right Atrial Dimensions (end-systolic area during ventricular systole), Left Ventricular Hypertrophy (Evaluation of left ventricular mass and relative wall thickness, assessment of dilation of Inferior Vena Cava (IVC), Pericardial Effusion (presence and extent), Valvular Insufficiencies (organic mitral and aortic regurgitations) and Pulmonary Pressures (Tricuspid regurgitation velocity (TRV) and systolic pulmonary arterial pressure (PAPs)). All parameters were indexed to body surface area (BSA) to ensure standardized comparisons.

2.4. Statistical analysis

Statistical analysis was conducted using SPSS software (IBM Corp., Armonk, NY, version 20.0). Continuous variables were compared using analysis of variance (ANOVA). The *t*-test was employed to compare continuous variables between groups. The Chi-square test was used to assess differences in distributions between males and females. A *p*-value <0.05 was considered statistically significant.

3. Results

We enrolled and analyzed 63 patients with SS, comprising 7 males and 56 females, reflecting the typical gender distribution of the disease in the general population. Males were diagnosed at an older age compared to females (M: 64 ± 16.6 years; F: 58.9 ± 14.1 years; $p = 0.450$). Demographic data and clinical characteristics of enrolled patients. Are shown in the Table 1.

Clinical symptoms were similar between sexes, with dry eye (83.6 %; M: 6/7, F: 45/54; $p = 0.678$) and dry mouth (80.3 %; M: 6/7, F: 43/54; $p = 0.582$) being the most common. Clinical manifestations are summarized in Table 2.

During the follow-up, 3 deaths occurred (4.8 %; M: 1/7, F: 2/56; $p = 0.302$). These findings, consistent with the study duration and sample size, suggest no significant association between gender and mortality risk.

Inflammatory markers (Table 2), including ESR and CRP, were positive in 15/38 patients (M: 0/4, F: 15/34) and 9/31 patients (M: 3/6, F: 6/25), respectively, with no significant differences between sexes (CRP: $p = 0.320$; ESR: $p = 0.138$). Antibody profiles revealed gender-based differences: ANA positivity was higher in females (M: 2/7, F: 41/55; $p = 0.024$), as were anti-Ro (SSA) Abs (M: 1/7, F: 39/56; $p = 0.008$). No significant differences were found for anti-La (SSB), ENA, anticentromere, or rheumatoid factor Cardiovascular risk factors were similar in both sexes. (Table 3).

We analyzed data from respiratory function tests, summarized in the Table 4. High-Resolution Computed Tomography (HRCT) was performed on 40 out of 63 patients, all of whom exhibited symptoms. Among these, 24 patients (60 %) were diagnosed with interstitial lung disease (ILD) (M: 3/7, F: 21/56; $p = 0.543$). Of the ILD-positive patients, 9 (37.5 %) also presented fibrosis on HRCT (M: 3/7, F: 6/56; $p = 0.054$).

The 6-Minute Walk Test (6MWT) was conducted in 18 of the 63 patients (28.6 %), and desaturation during the test was observed in 6/18 (33.3 %) (M: 2/3, F: 4/15; $p = 0.245$). The distance covered during the 6MWT ranged from 160 to 460 m, with a mean of 345.29 ± 80.09 m (M: 340 ± 60 m; F: 346 ± 85 m; $p = 0.884$).

Forced Vital Capacity (FVC%) values averaged 102.36 ± 19.7 %, ranging from 46 to 153 % (M: 88.0 ± 6.4 %; F: 104.3 ± 20.18 %; $p = 0.005$). Absolute FVC values averaged 2.46 ± 0.74 L and was significantly higher in males (M: 3.05 ± 0.19 L; F: 2.38 ± 0.76 L; $p = 0.001$). Forced Expiratory Volume in 1 s (FEV_1) did not reach statistical significance (M: 2.46 ± 0.10 L; F: 1.87 ± 0.60 L; $p = 0.063$) but showed a trend toward higher values in males.

Total Lung Capacity (TLC) was significantly higher in males (M: 6.03 ± 0.57 L; F: 4.67 ± 1.14 L; $p = 0.006$). Residual Volume (RV) was also significantly higher in males (M: 2.98 ± 0.38 L; F: 2.36 ± 0.56 L; $p = 0.036$).

Diffusing capacity for carbon monoxide (DLCO%) averaged 60.9 ± 21 %, and absolute DLCO values ranged from 4.3 to 1.58. Both DLCO% (M: 52.5 ± 21.6 %; F: 62.2 ± 21.1 %; $p = 0.450$) and absolute DLCO (M: 4.16 ± 1.93; F: 4.36 ± 1.56; $p = 0.852$) were not significantly different between sexes.

Comparison of echocardiographic parameters (Table 5) revealed no significant increase in tricuspid valve regurgitation velocity (TVR), with values of 2.28 ± 0.24 m/s in males and 2.31 ± 0.55 m/s in females ($p = 0.844$). Similarly, pulmonary arterial systolic pressure (PAPs) values were not elevated (29.3 ± 4.2 mmHg vs. 27.9 ± 12.3 mmHg, $p = 0.558$), excluding pulmonary hypertension as a significant factor in these patients.

The TAPSE/PAPs ratio was higher in females but not statistically significant (0.90 ± 0.28 vs. 0.94 ± 0.37, $p = 0.696$). Right ventricular systolic function, assessed via TAPSE, was higher in males (25.6 ± 5.6

Table 2
Frequency of symptoms, and immune-hematologic parameters of the patients enrolled in the study, stratified according to gender. *p*-values refer to differences between genders; significant p- values are in bold.

	Total	Males	Females	p-value
Dry eyes	51/61	6/7	45/54	0.678
Dry mouth	49/61	6/7	43/54	0.582
Arthralgia	10/28	1/1	9/27	0.357
Raynaud's phenomenon	10/63	1/7	9/56	0.694
ANA	43/62	2/7	41/55	**0.024**
Anti SSA (anti-Ro) ab	40/63	1/7	39/56	**0.008**
Anti SSB (anti-La) ab	21/63	1/7	20/56	0.408
ENA	29/60	1/7	28/53	0.104
Anti Centromer ab	1/50	0/7	1/43	0.860
Rheumatoid phenomena	25/58	3/7	22/51	0.656
CRP	9/31	3/6	6/25	0.320
ESR	15/38	0/4	15/34	0.138

Table 3
Frequency of cardiovascular risk factors in the patients enrolled in the study, stratified according to gender. p-values refer to differences between genders.

	Total	Males	Females	p value
BMI > 30	12/63	1/7	11/56	0.600
Diabetes	4/60	1/7	3/53	0.399
Dyslipidemia	15/62	2/7	13/55	0.545
Current smoker	5/63	1/7	4/56	0.457
Former smoker	12/63	4/7	8/56	0.210
IR chronic	5/54	2/7	3/47	0.120
Hypertension	20/60	2/7	18/54	0.584

Table 4
Respiratory function parameters measured in the patients enrolled in the study, stratified according to gender. p-values refer to differences between genders; significant p values are in bold.

	Total	Males	Females	P value
HRTC	40/63	5/7	35/56	0.494
ILD	24/63	3/7	21/56	0.543
FIBROSIS	9/63	3/7	6/56	**0.054**
6MWT	18/63			
DESCRIPTION		2/3	4/15	0.245
6MWT METERS	345.29 ± 80.08	340 ± 60	346 ± 85	0.884
FVC	2.46 ± 7.4	3.05 ± 0.19	2.38 ± 0.76	**0.001**
FVC%	102.36 ± 19.7	88 ± 6.4	104 ± 20	**0.005**
FEV1	1.94 ± 0.6	2.5 ± 0.1	1.87 ± 0.6	**0.063**
DLCO	4.3–1.58	4.16 ± 1.93	4.36 ± 1.56	0.852
DLCO%	60.9 ± 21	52.5 ± 21.6	62.20 ± 21.1	0.450
TLC	4.85 ± 1.17	6.03 ± 0.57	4.68 ± 1.14	**0.006**
RV	2.44 ± 0.58	2.98 ± 0.38	2.36 ± 0.56	**0.036**

Table 5
Echocardiographic parameters measured in the patients enrolled in the study, stratified according to gender. p-values refer to differences between genders; significant p values are in bold in bold.

	Total	Males	Females	P value
Adx AREA (cm^2)	13.93 ± 3.18	14.8 ± 3.40	13.8 ± 3.17	0.537
Adx VOLUME (ml)	32.84 ± 13.39	35.8 ± 12.5	32.5 ± 13.6	0.569
FAC Vdx (%)	40.17 ± 10.20	34.2 ± 11.4	40.9 ± 9.9	0.216
FE Vdx 3D (%)	48.24 ± 6.70	55.5 ± 6.6	59.7 ± 5.1	0.587
FWLS Vdx (%)	−23.18 ± 11.8	−24.7 ± 3.20	−23 ± 12.7	0.560
4CLS Vdx (%)	−18.97 ± 9.52	−19.6 ± 2.64	−18.9 ± 10.2	0.770
TAPSE (mm)	23.40 ± 4.15	25.6 ± 5.6	23.1 ± 3.9	0.300
S′ (TDI) (cm/s)	13.41 ± 8.45	13 ± 2.38	13.5 ± 8.94	0.736
TRICUSPID VELOCITY TVR (m/s)	2.30 ± 0.53	2.28 ± 0.24	2.31 ± 0.55	0.844
PAPs (mmHg)	28.08 ± 11.64	29.3 ± 4.2	27.9 ± 12.3	0.558
TAPSE/PAPs	0.94 ± 0.36	0.90 ± 0.28	0.94 ± 0.37	0.696
NOTCH	3/53	/	3/53	0.760
VCI (mm)	15.31 ± 3.48	17.2 ± 2.74	15.1 ± 3.5	0.124
POLMONAR ARTERY DIAMETER (mm)	20.35 ± 3.77	22.5 ± 3.8	20.1 ± 3.7	**0.046**
POLMONAR ARTERY ACCELERATION (ms)	149.09 ± 74.5	121 ± 44.2	151 ± 76	0.369
TVI-RVOT	18.33 ± 14.61	38.3 ± 46.9	16.5 ± 6.26	**0.003**
VOLUME max Asx 3D	62.89 ± 22.04	84.5 ± 22.1	59.7 ± 20.4	**0.040**
VOLUME min Asx 3D	25.17 ± 14.83	42.5 ± 26.6	22.6 ± 10.6	**0.001**
TELEDIASTOLIC DIAMETER Vsx.	45.38 ± 4.70	51.0 ± 3.0	44.7 ± 4.40	**0.001**
MASS 2D	70.87 ± 16.93	86.6 ± 20.4	68.9 ± 15.6	**0.064**
TELEDIASTOLIC VOLUME 2D Vsx.	84.78 ± 24.33	106 ± 35.4	81.99 ± 21.4	**0.013**
FE 2D	57.34 ± 4.68	55.1 ± 2.44	57.6 ± 4.83	**0.041**

mm vs. 23.1 ± 3.9 mm, $p = 0.300$) but without statistical significance. Tissue Doppler imaging (TDI) of the systolic excursion (S′) showed no significant differences between sexes ($p = 0.736$) and was slightly higher in females (M: 13 ± 2.38; F: 13.5 ± 8.94).

Inferior vena cava (IVC) diameter was non-dilated ($p = 0.124$) and higher in males (M: 17.2 ± 2.74 mm; F: 15.1 ± 3.5 mm). Right atrial area and volume were similar between groups, with no evidence of dilation (Area: M: 14.8 ± 3.40 cm^2 vs. F: 13.8 ± 3.17 cm^2, $p = 0.537$; Volume: M: 35.8 ± 12.5 mL vs. F: 32.5 ± 13.6 mL, $p = 0.569$). Fractional area change (FAC) of the right ventricle was higher in females (M: 34.2 ± 11.4 %; F: 40.9 ± 9.9 %) but did not reach statistical significance ($p = 0.216$).

In the left heart chambers, significant dilation was observed in males, as indicated by higher 3D-minimal left atrial volume (LAV-min-3D) and 3D-maximal left atrial volume (LAV-max-3D) values (LAV-min-3D: M: 42.5 ± 26.6 mL vs. F: 22.6 ± 10.6 mL, $p = 0.001$; LAV-max-3D: M: 84.5 ± 22.1 mL vs. F: 59.7 ± 20.4 mL, $p = 0.040$), as expected. Left ventricular end-diastolic diameter and volume were also significantly larger in males (End-diastolic diameter: M: 51.0 ± 3.0 mm vs. F: 44.7 ± 4.40 mm, $p = 0.001$; End-diastolic volume: M: 106 ± 35.4 mL vs. F: 81.99 ± 21.4 mL, $p = 0.013$).

The 2D ejection fraction (EF) was significantly higher in females (M: 55.1 ± 2.44 % vs. F: 57.6 ± 4.83 %, $p = 0.041$). Conversely, 3D EF of the right ventricle showed no significant difference ($p = 0.587$) but was slightly higher in females (M: 55.5 ± 6.6 %; F: 59.7 ± 5.1 %). Left ventricular mass was greater in males (M: 86.6 ± 20.4 g vs. F: 68.9 ± 15.6 g, $p = 0.064$), approaching statistical significance and warranting further monitoring.

Pulmonary artery acceleration time was longer in females (M: 121 ± 44.2 ms vs. F: 151 ± 76 ms, $p = 0.369$) but not statistically significant. However, pulmonary artery diameter was significantly larger in males (M: 22.5 ± 3.8 mm vs. F: 20.1 ± 3.6 mm, $p = 0.046$), potentially attributable to their higher body surface area (BSA). Right ventricular outflow tract time-velocity integral (TVI-RVOT) was significantly higher in males (M: 38.3 ± 22.1 cm vs. F: 16.5 ± 6.26 cm, $p = 0.003$), suggesting a possible early increase in pulmonary pressures when combined with the pulmonary artery acceleration data.

No significant presence of NOTCHE was observed ($p = 0.760$), occurring in 3/53 females and 0/7 males. Speckle-tracking analysis of right ventricular strain revealed no significant differences between males and females for free wall longitudinal strain (FWLS: M: −24.7 ± 3.20 % vs. F: −23 ± 12.7 %, $p = 0.560$) or four-chamber longitudinal strain (4CLS: M: −19.6 ± 2.64 % vs. F: −18.9 ± 10.2 %, $p = 0.770$).

4. Discussion

In this study, we investigated the presence of pulmonary hypertension (pH) in a cohort of patients with SS treated at the Modena University Hospital. Additionally, we analyzed gender-based differences in rheumatologic, pulmonary, and cardiologic parameters.

PH in primary SS has historically been considered uncommon; however, varying diagnostic criteria have led to discrepancies in reported prevalence. Recent studies utilizing echocardiography as a screening tool have yielded conflicting results, leaving the true prevalence uncertain [22,23]. In our study, only 1 out of 63 patients was diagnosed with precapillary pulmonary hypertension, confirmed through right heart catheterization, revealing a lower prevalence of PH compared to studies relying exclusively on echocardiographic criteria. Our findings differ from some previous studies on PH prevalence in the SS population, likely due to differences in diagnostic criteria and study methodologies. For instance, the study by Senol Kobak reported pulmonary hypertension in 11 out of 47 patients (23.4 %) [22]. This discrepancy may be attributed to several factors. First, previous studies used a screening threshold of SPAP >30 mmHg, whereas our cohort's PAP values did not meet this criterion, potentially accounting for the differences in reported prevalence. Second, the demographic characteristics of the study populations differed: our cohort primarily consisted of Caucasian patients, whereas the Senol Kobak study focused on a Turkish population. Third, the earlier study controlled for medication effects by discontinuing drugs that might influence echocardiographic readings, a factor not accounted for in our study. This underscores the importance of an accurate invasive assessment even in cases where indirect indices would unequivocally suggest the presence of PH, considering that echocardiographic estimates of pulmonary pressure can be influenced by various factors, such as right ventricular preload and image quality. Similar variations in PH prevalence have been observed in other connective tissue diseases, including systemic sclerosis, mixed connective tissue disease, systemic lupus erythematosus, and rheumatoid arthritis, suggesting a broader pattern influenced by disease-specific and demographic factors. Notably, studies have reported variations in PH prevalence and severity across different populations, potentially influenced by genetic, environmental, and healthcare-related factors [24–26]. As noted earlier, prior studies used SPAP >30 mmHg as a threshold, while our cohort had lower PAP values, which may partly explain the observed discrepancies in prevalence. This discrepancy between our results and those of previous studies may reflect several methodological aspects: our study applied stringent diagnostic criteria and excluded patients with coexisting conditions that might have

influenced pulmonary pressure, potentially contributing to differences in reported prevalence Differences in ethnicity, age distribution, and cardiovascular risk profiles likely contribute to variability in PH prevalence among SS patients, emphasizing the need for cautious comparisons across studies.

It is important to note that an additional patient exhibited echocardiographic values at the upper limit of normal and was scheduled for right heart catheterization but ultimately declined the procedure. Both patients diagnosed with or suspected of PH also had SS associated with interstitial lung disease (ILD). Larger-scale studies will be necessary to establish the true prevalence of PH in European populations.

The secondary aim of this study was to evaluate differences between male and female patients with respect to rheumatologic, pulmonary, and cardiologic parameters. From a rheumatologic perspective, we observed significant gender differences in the prevalence of certain autoantibodies. Females showed a significantly higher prevalence of ANA positivity (M: 2/7; F: 41/55; $p = 0.024$) and SSA (anti-Ro) antibodies (M: 1/7; F: 39/56; $p = 0.008$). Conversely, no significant differences were noted for SSB (anti-La) autoantibodies (M: 1/7; F: 20/56; $p = 0.408$) or ENA autoantibodies (M: 1/7; F: 28/53; $p = 0.620$). Our findings agree with existing literature, which consistently reports that women with SS exhibit a higher frequency of immunological manifestations, including ANA and SSA positivity, compared to men. This discrepancy may be attributed to hormonal influences, particularly the role of estrogen in immune modulation. Estrogen has been shown to activate B cells, leading to increased autoantibody production, which contributes to the higher prevalence of autoimmune diseases in women [27]. Even after menopause, lower levels of estrogen remain sufficient to promote B cell proliferation and autoantibody production, supporting the observed higher autoantibody positivity rates among postmenopausal women. These findings suggest that the effect of sex hormones, rather than age, underlies the immunological differences between male and female patients with SS [28,29].

This study demonstrated greater impairment in pulmonary function among males compared to females. Forced vital capacity (FVC) and the percentage of predicted FVC (FVC%) were both notably lower in males. Additional differences were observed in total lung capacity (TLC) and residual volume (RV), with males showing higher values for both parameters. Forced expiratory volume in 1 s (FEV_1) was also reduced in males compared to females, indicating a potential trend, though it did not reach statistical significance. The FEV_1/FVC ratio (Tiffeneau index), which assesses lung elasticity and is particularly relevant in the presence of fibrosis, did not show significant differences between genders. These findings align with the literature, which underscores the importance of FVC, FVC%, and FEV_1 in monitoring the progression of pulmonary fibrosis [30]. Declines in these values are associated with worsening fibrosis and higher mortality risk. Specifically, FVC serves as a critical marker of disease progression, while lower FVC% values correlate with long-term mortality. No significant differences were found in the diffusing capacity of the lungs for carbon monoxide (DLCO), consistent with prior studies [31]. Thus, males exhibited reduced lung volumes and impaired respiratory function, likely associated with the higher prevalence of pulmonary fibrosis in this group. This suggests that fibrosis may significantly contribute to the observed differences in pulmonary function between sexes.

Analysis of echocardiographic data revealed no significant differences between males and females in the right heart sections, including atrial area, atrial volume, right ventricular systolic function (assessed through FAC, TAPSE, S′, and right ventricular strain parameters), or pulmonary pressure estimates such as pulmonary arterial pressure (PAPs), tricuspid regurgitation velocity, and pulmonary artery acceleration time. These findings suggest similar functional profiles between the two groups regarding right-sided cardiac function under non-pathological conditions.

Interestingly, in our study, the Vmax of tricuspid regurgitation was slightly higher in females than in males, while the inferior vena cava diameter was comparable between the two groups. However, pulmonary systolic pressure (PAPs) was marginally higher in males than in females (29.3 ± 4.2 mmHg vs. 27.9 ± 12.3 mmHg, $p = 0.558$), although it did not reach statistical significance. This apparent discrepancy could be explained by various physiological and methodological factors. First, variations in cardiac morphology between sexes could play a role, as males had a more dilated left ventricle and a greater end-diastolic volume, which could influence the transmission of pressure in the pulmonary circulation. Second, the Influence of ventricular compliance and afterload, as the greater left ventricular mass in males could contribute to an increase in pulmonary pressure secondary to altered diastolic function. Finally, we emphasize that in our study, no patient had a PAPs value clearly indicative of significant pulmonary hypertension, as confirmed by right heart catheterization in doubtful cases.

We also reported some interesting differences between sexes. Pulmonary artery diameter was larger in males, potentially linked to a higher body surface area (BSA), and alterations in this measurement could indicate early signs of disease. Additionally, males exhibited significantly altered TVI-RVOT values, which may reflect early hemodynamic changes. These findings could be associated with the higher prevalence of fibrosis in males, which appears to impact the right heart sections [32].

Contrary to previous reports suggesting significant right ventricular remodeling and dysfunction in the presence of fibrosis, this phenomenon was not prominent in our study. This discrepancy may stem from the low prevalence of pulmonary hypertension in our cohort, which is a major driver of right heart deterioration [33,34].

In contrast, left-sided cardiac parameters showed more pronounced gender differences. Males exhibited greater left atrial dilatation and altered function, with larger maximum and minimum left atrial volumes. Additionally, males demonstrated increased left ventricular end-diastolic diameter and volume, indicating structural remodeling. Although the values fall within the normal range, our aim was to emphasize that male SS patients showed a tendency toward greater dilation and increased left ventricular mass, which could be related to early diastolic dysfunction, as also suggested by differences in atrial volumes and pulmonary function parameters.

We believe that, in the context of our specific cohort, these findings may suggest a male predisposition to more pronounced cardiac remodeling. These findings suggest that left ventricular diastolic dysfunction, potentially progressing to systolic dysfunction [35], may be more prominent in males with fibrosis.

From a pathophysiological perspective, testosterone has been implicated in promoting fibrosis, vascular calcification, and plaque formation through its interaction with the Gas6 pathway, particularly in older individuals, increasing the cardiovascular risk of atherosclerosis, coronary artery disease, and cardiovascular events [36,37]. This aligns with the observed alterations in the male group, where the mean age was higher at disease onset. Conversely, estrogen in females may offer cardioprotective effects, reducing fibrosis and supporting cardiac remodeling [38], as evidenced by fewer structural and functional changes in the female cohort.

Another significant observation was that several echocardiographic and pulmonary parameters suggested a distinct pattern of cardiac remodeling in males. Specifically, the reduced ejection fraction observed in men, while still within normal limits, aligns with the greater fibrosis burden reported in previous studies [28,29], indicating subclinical myocardial changes rather than overt dysfunction. Additionally, trends in left ventricular mass suggest a potential predisposition to hypertrophy in males, further supporting the hypothesis of progressive remodeling.

Beyond structural changes, pulmonary parameters may also reflect sex-specific adaptations, as alterations in pulmonary vascular resistance and right ventricular function could contribute to the observed disparities. These findings emphasize the differential impact of sex on cardiac and pulmonary remodeling in patients with fibrosis. Males appear more vulnerable to structural and functional alterations, likely driven by

testosterone-mediated pathways [26], whereas females may benefit from the cardioprotective effects of estrogen, mitigating the extent of remodeling.

This highlights the necessity of adopting gender-specific approaches in the assessment and management of cardiac involvement, ensuring that subtle yet clinically relevant changes are identified and addressed in a timely manner. Further research is warranted to elucidate the long-term implications of these findings and to refine therapeutic strategies accordingly.

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CRediT authorship contribution statement

Francesca Coppi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Alessia Cavalletti:** Methodology, Investigation. **Gianluca Pagnoni:** Methodology, Investigation, Formal analysis. **Cecilia Campani:** Methodology, Investigation. **Francesca Grossule:** Methodology, Investigation. **Arianna Maini:** Investigation, Formal analysis, Data curation. **Pierluca Macripò:** Methodology, Investigation. **Giada Zanini:** Methodology, Investigation. **Giorgia Sinigaglia:** Methodology, Investigation. **Dilia Giuggioli:** Writing – review & editing, Investigation, Funding acquisition. **Milena Nasi:** Writing – review & editing, Formal analysis, Data curation. **Francesco Fedele:** Writing – review & editing, Conceptualization. **Anna Vittoria Mattioli:** Writing – review & editing, Project administration, Funding acquisition. **Giuseppe Boriani:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Marcello Pinti:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

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