



Predicting Pulmonary Arterial Hypertension in Patients with Connective Tissue Disease: A Systematic Review of Risk Factors and Screening Strategies

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ABSTRACT

Introduction: Pulmonary arterial hypertension (PAH) is a severe and life-threatening complication of connective tissue diseases (CTD), associated with significant morbidity and mortality. Early detection through effective screening strategies and identification of robust risk factors is crucial for improving patient outcomes. This systematic review aims to synthesize and evaluate the current evidence on risk factors, predictors, and screening strategies for PAH in patients with CTD.

Methods: A systematic literature search was conducted to identify studies investigating risk factors, biomarkers, screening strategies, and predictive models for PAH in CTD patients. Studies were included if they enrolled patients with systemic sclerosis (SSc), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), or other CTDs, and reported quantitative measures of association or screening performance. Data were extracted on CTD populations, PAH definitions, risk factors, screening modalities, and predictive performance metrics.

Results: Fifty-four studies met inclusion criteria, encompassing prospective and retrospective cohorts, systematic reviews, and meta-analyses. The majority focused on SSc (n=38), followed by SLE (n=8) and MCTD (n=1). Composite screening algorithms (DETECT and ASIG) demonstrated superior performance (sensitivity 94-100%, NPV 87-100%) compared to single modalities. Echocardiography showed moderate sensitivity (49-95%) with threshold-dependent specificity (43-100%). NT-proBNP exhibited pooled sensitivity of 67% (95% CI 52-79%) and specificity of 84% (95% CI 75-91%). In SSc, key risk factors included low DLCO (45-70% predicted), anti-centromere antibodies, telangiectasias, and nailfold capillaropathy (OR 7.3, 95% CI 3.0-18.0). In SLE, anti-RNP antibody (OR 3.68, 95% CI 2.04-6.63), antiphospholipid antibodies (OR 2.28, 95% CI 1.65-3.15), Raynaud's phenomenon (RR 1.83, 95% CI 1.41-2.37), and interstitial lung disease (RR 4.36, 95% CI 2.42-7.85) were significant predictors. Survival was worse in SSc-PAH (67% at 3 years) compared to SLE-PAH (87% at 3 years). Screening programs improved survival outcomes compared to clinical diagnosis.

Discussion: This systematic review demonstrates that multi-modal screening algorithms significantly outperform single-modality approaches for CTD-PAH detection. Risk factor profiles differ substantially between CTD subtypes, reflecting distinct underlying pathophysiological mechanisms. The predominance of SSc-focused evidence highlights a critical research gap for non-scleroderma CTDs. The integration of emerging modalities including exercise testing, nailfold capillaroscopy, and genetic risk scores may further refine risk stratification.

Conclusion: Current evidence supports annual multi-modal screening in SSc patients using composite algorithms incorporating echocardiography, pulmonary function tests, and biomarkers. For SLE and other CTDs, targeted screening based on identified risk factor profiles is recommended. Future research should focus on validating prediction models in diverse CTD populations and investigating early intervention strategies in high-risk patients.

Keywords: Pulmonary arterial hypertension; connective tissue disease; systemic sclerosis; systemic lupus erythematosus; screening; risk factors; biomarkers; echocardiography

INTRODUCTION

Background

Pulmonary arterial hypertension (PAH) represents one of the most devastating complications of connective tissue diseases (CTD), characterized by progressive remodeling of small pulmonary arteries leading to right heart failure and premature death [1, 2]. Among the various CTD subtypes, systemic sclerosis (SSc) carries the highest risk of PAH development, with a reported prevalence of 8-12%, followed by mixed connective tissue disease (MCTD) and systemic lupus erythematosus (SLE) [3, 4]. The prognosis of CTD-PAH has historically been poorer than that of idiopathic PAH, with three-year survival rates of approximately 62% compared to 72% in the general PAH population [1, 40].

The pathogenesis of CTD-PAH is complex and multifactorial, involving vasculopathy, inflammation, fibrosis, and in some cases, thrombotic mechanisms that vary across different CTD subtypes [5, 7]. In SSc, the predominant pathology is a fibroproliferative vasculopathy with concentric intimal fibrosis and medial hypertrophy, whereas SLE-PAH often exhibits an inflammatory component with potential responsiveness to immunosuppressive therapy [8, 28]. This heterogeneity in underlying mechanisms necessitates CTD-specific approaches to risk stratification and screening.

Early detection of PAH in CTD patients is critical, as delayed diagnosis is associated with advanced hemodynamic compromise and worse survival outcomes [12, 15]. The implementation of systematic screening programs has been shown to identify patients at an earlier, milder stage of disease when therapeutic interventions may be more effective [12, 32]. However, the optimal screening strategy remains debated, with various modalities including echocardiography, pulmonary function tests, biomarkers, and composite algorithms being proposed [2, 3, 16].

Research Gap

Despite the availability of multiple screening guidelines and an expanding body of literature on CTD-PAH, several critical knowledge gaps persist. First, the majority of published research has

focused predominantly on SSc, with limited data available for other CTD subtypes such as SLE, MCTD, dermatomyositis, and Sjögren's syndrome [7, 10]. This disparity raises questions about the generalizability of current screening recommendations to non-scleroderma CTD populations. Second, while numerous individual risk factors have been identified across studies, the comparative strength and consistency of these factors across different CTD subtypes have not been comprehensively synthesized [7, 11]. Third, the performance characteristics of various screening modalities have been reported with considerable heterogeneity, and the relative superiority of composite algorithms versus single-modality approaches requires systematic evaluation [2, 3, 16]. Fourth, emerging screening tools including exercise testing, nailfold capillaroscopy, and artificial intelligence-based approaches have shown promise but lack standardized implementation guidelines [6, 19, 50]. Finally, the impact of early detection through screening programs on long-term clinical outcomes, including survival, warrants comprehensive synthesis of available evidence [12].

Novelty

This systematic review provides several novel contributions to the existing literature. First, it offers a comprehensive synthesis of evidence across all CTD subtypes, enabling direct comparison of risk factor profiles and screening performance between SSc, SLE, MCTD, and other connective tissue diseases. Second, it integrates findings from traditional screening modalities with emerging technologies including nailfold videocapillaroscopy, exercise hemodynamics, and genetic risk stratification, providing a forward-looking perspective on the future of CTD-PAH prediction. Third, it systematically evaluates the performance of composite screening algorithms (DETECT and ASIG) against single-modality approaches, quantifying the incremental benefit of multi-parametric strategies. Fourth, it synthesizes survival data from multiple international registries to provide updated estimates of CTD-PAH prognosis and temporal trends in outcomes. Fifth, it identifies CTD-specific risk factor patterns that reflect underlying pathophysiological differences, supporting the rationale for tailored screening approaches.

Research Objectives

The primary objectives of this systematic review are: (1) to identify and synthesize all reported risk factors for PAH development in patients with various CTD subtypes; (2) to evaluate

the performance characteristics of different screening modalities including echocardiography, pulmonary function tests, biomarkers, and composite algorithms; (3) to compare risk factor profiles and screening effectiveness across different CTD populations; (4) to assess the impact of screening programs on clinical outcomes including survival; and (5) to identify evidence gaps and provide recommendations for future research directions.

Hypotheses

Based on the existing literature, we hypothesized that: (1) composite screening algorithms would demonstrate superior sensitivity and negative predictive value compared to any single screening modality; (2) risk factor profiles would differ significantly between SSc and SLE, reflecting distinct underlying pathogenic mechanisms; (3) screening-detected PAH would be associated with better survival outcomes compared to clinically diagnosed PAH; and (4) emerging modalities including nailfold capillaroscopy and exercise testing would provide incremental predictive value beyond conventional screening tools.

Benefits of the Study

This systematic review has several important clinical and research implications. For clinicians, it provides a comprehensive evidence base to inform screening practices and risk stratification in CTD patients, potentially enabling earlier detection and treatment of PAH. The identification of CTD-specific risk factors may facilitate targeted screening of high-risk patients, improving resource allocation and cost-effectiveness. For researchers, it highlights critical evidence gaps and identifies priorities for future investigation, including the need for prospective validation of prediction models in diverse CTD populations and the development of standardized protocols for emerging screening modalities. For patients, improved screening strategies may lead to earlier diagnosis, better functional outcomes, and enhanced survival.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This

approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Predicting Pulmonary Arterial Hypertension in Patients with Connective Tissue Disease: A Systematic Review of Risk Factors and Screening Strategies.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Target Population:** Does the study include patients diagnosed with connective tissue diseases (systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, dermatomyositis, polymyositis, Sjögren's syndrome, or overlap syndromes) AND can results for this population be analyzed separately from other patient groups?
- **Research Focus:** Does the study investigate risk factors, predictors, biomarkers, or screening strategies for pulmonary arterial hypertension?
- **PAH Outcome Definition:** Does the study have clearly defined PAH outcomes confirmed by right heart catheterization or echocardiography with established diagnostic criteria, AND does it focus specifically on PAH (Group 1 pulmonary hypertension) rather than other forms of pulmonary hypertension?
- **Quantitative Measures:** Does the study report quantitative measures of association, predictive performance, or screening effectiveness (such as odds ratios, hazard ratios, sensitivity/specificity, or predictive values)?
- **Study Design and Sample Size:** Is the study a longitudinal cohort study, case-control study, cross-sectional study with predictive modeling, randomized controlled trial, systematic review, or meta-analysis with adequate sample size (≥ 20 participants for primary studies)?

- **Study Purpose:** Does the study address prediction or screening for PAH (rather than focusing exclusively on treatment or management of established PAH without any predictive/screening component)?
- **Study Type:** Is the study NOT an animal study, in vitro study, case report, case series with <20 patients, editorial, commentary, or conference abstract?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention / Index Test)	C (Comparison/Context)	O (Outcome)
Keyword 1	Connective Tissue Disease	Risk Factors	Diagnostic Accuracy	Pulmonary Arterial Hypertension
Keyword 2	CTD	Predictors	Predictive Performance	PAH
Keyword 3	Mixed Connective Tissue Disease	Echocardiography	Screening Accuracy Studies	Pulmonary Artery Pressure
Keyword 4	MCTD	Biomarkers	Screening Population	Prognosis

The Boolean MeSH keywords inputted on databases for this research are: ("*Connective Tissue Disease*" OR "*CTD*" OR "*Mixed Connective Tissue Disease*" OR "*MCTD*") AND ("*Risk Factors*" OR "*Predictors*" OR "*Echocardiography*" OR "*Biomarkers*") AND ("*Diagnostic Accuracy*" OR "*Predictive Performance*" OR "*Screening Accuracy Studies*" OR "*Screening*")

Population") AND ("Pulmonary Arterial Hypertension" OR "PAH" OR "Pulmonary Artery Pressure" OR "Prognosis")

Data extraction

- **CTD Population:**

Extract details about the connective tissue disease population studied for PAH prediction, including:

- Specific CTD types (systemic sclerosis, SLE, mixed connective tissue disease, etc.)
- Sample size
- Age range and mean age
- Gender distribution
- Disease duration
- Disease severity or subtype classifications
- Inclusion/exclusion criteria specific to CTD patients

- **PAH Definition:**

Extract how pulmonary arterial hypertension was defined and diagnosed in CTD patients, including:

- Diagnostic criteria used (hemodynamic thresholds, imaging findings)
- Diagnostic methods (right heart catheterization, echocardiography, etc.)
- Timing of PAH diagnosis relative to CTD diagnosis
- PAH severity classifications if provided

- Any CTD-specific PAH diagnostic considerations

- **Risk Factors:**

Extract all risk factors identified for predicting PAH development in CTD patients, including:

- Clinical risk factors (symptoms, physical exam findings)
- Laboratory biomarkers and their values
- Imaging findings (chest X-ray, CT, echocardiographic parameters)
- CTD-specific factors (autoantibodies, organ involvement patterns)
- Demographic factors
- Temporal relationships between risk factors and PAH development

- **Risk Prediction Performance:**

Extract statistical measures of how well identified risk factors predict PAH in CTD patients, including:

- Odds ratios or hazard ratios with confidence intervals
- Sensitivity and specificity values
- Positive and negative predictive values
- Area under the curve (AUC) for predictive models
- P-values and statistical significance
- Performance of combined risk factor models vs. individual factors

- **Screening Strategies:**

Extract details about screening strategies used to detect PAH in CTD patients, including:

- Specific screening methods (echocardiography protocols, biomarker panels, imaging approaches)
- Screening frequency and timing recommendations
- Multi-step screening algorithms
- Screening thresholds and cut-off values
- Integration with routine CTD care
- Cost-effectiveness considerations if mentioned

- **Screening Performance:**

Extract performance metrics for PAH screening strategies in CTD patients, including:

- Sensitivity and specificity of screening methods
- Positive and negative predictive values
- False positive and false negative rates
- Time to PAH detection
- Comparison of different screening approaches
- Performance in different CTD subtypes
- Screening accuracy compared to gold standard diagnosis

- **Study Design:**

Extract methodology details relevant to PAH prediction research in CTD patients, including:

- Study design (cohort, case-control, cross-sectional)
- Follow-up duration and frequency
- Sample size and power calculations
- Multicenter vs. single-center design
- Prospective vs. retrospective data collection
- Validation of findings (internal/external validation)
- Statistical analysis methods for prediction modeling

- **Key Findings:**

Extract the main conclusions about predicting PAH in CTD patients, including:

- Most significant risk factors or screening approaches identified
- Recommended prediction or screening protocols
- Clinical implications for CTD patient management
- Limitations acknowledged by authors
- Generalizability to different CTD populations
- Recommendations for future research in CTD-PAH prediction

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Connective Tissue Disease" OR "CTD" OR "Mixed Connective Tissue Disease" OR "MCTD") AND ("Risk Factors" OR "Predictors" OR "Echocardiography" OR "Biomarkers") AND ("Diagnostic Accuracy" OR "Predictive Performance" OR "Screening Accuracy Studies" OR "Screening Population") AND ("Pulmonary Arterial Hypertension" OR "PAH" OR "Pulmonary Artery Pressure" OR "Prognosis")</i>	6
Semantic Scholar	<i>("Connective Tissue Disease" OR "CTD" OR "Mixed Connective Tissue Disease" OR "MCTD") AND ("Risk Factors" OR "Predictors" OR "Echocardiography" OR "Biomarkers") AND ("Diagnostic Accuracy" OR "Predictive Performance" OR "Screening Accuracy Studies" OR "Screening Population") AND ("Pulmonary Arterial Hypertension" OR "PAH" OR "Pulmonary Artery Pressure" OR "Prognosis")</i>	2
Springer	<i>("Connective Tissue Disease" OR "CTD" OR "Mixed Connective Tissue Disease" OR "MCTD") AND ("Risk Factors" OR "Predictors" OR "Echocardiography" OR "Biomarkers") AND ("Diagnostic Accuracy" OR "Predictive Performance" OR "Screening Accuracy Studies" OR "Screening Population") AND ("Pulmonary Arterial Hypertension" OR "PAH" OR "Pulmonary Artery Pressure" OR "Prognosis")</i>	860
Google Scholar	<i>("Connective Tissue Disease" OR "CTD" OR "Mixed Connective Tissue Disease" OR "MCTD") AND ("Risk Factors" OR "Predictors" OR "Echocardiography" OR "Biomarkers") AND ("Diagnostic Accuracy" OR "Predictive Performance" OR "Screening Accuracy Studies" OR "Screening Population") AND ("Pulmonary Arterial Hypertension" OR "PAH" OR "Pulmonary Artery Pressure" OR "Prognosis")</i>	6,280
Wiley Online Library	<i>("Connective Tissue Disease" OR "CTD" OR "Mixed Connective Tissue Disease" OR "MCTD") AND ("Risk Factors" OR "Predictors" OR "Echocardiography" OR "Biomarkers") AND ("Diagnostic Accuracy" OR "Predictive Performance" OR "Screening Accuracy Studies" OR "Screening Population") AND ("Pulmonary Arterial Hypertension" OR "PAH" OR "Pulmonary Artery Pressure" OR "Prognosis")</i>	938

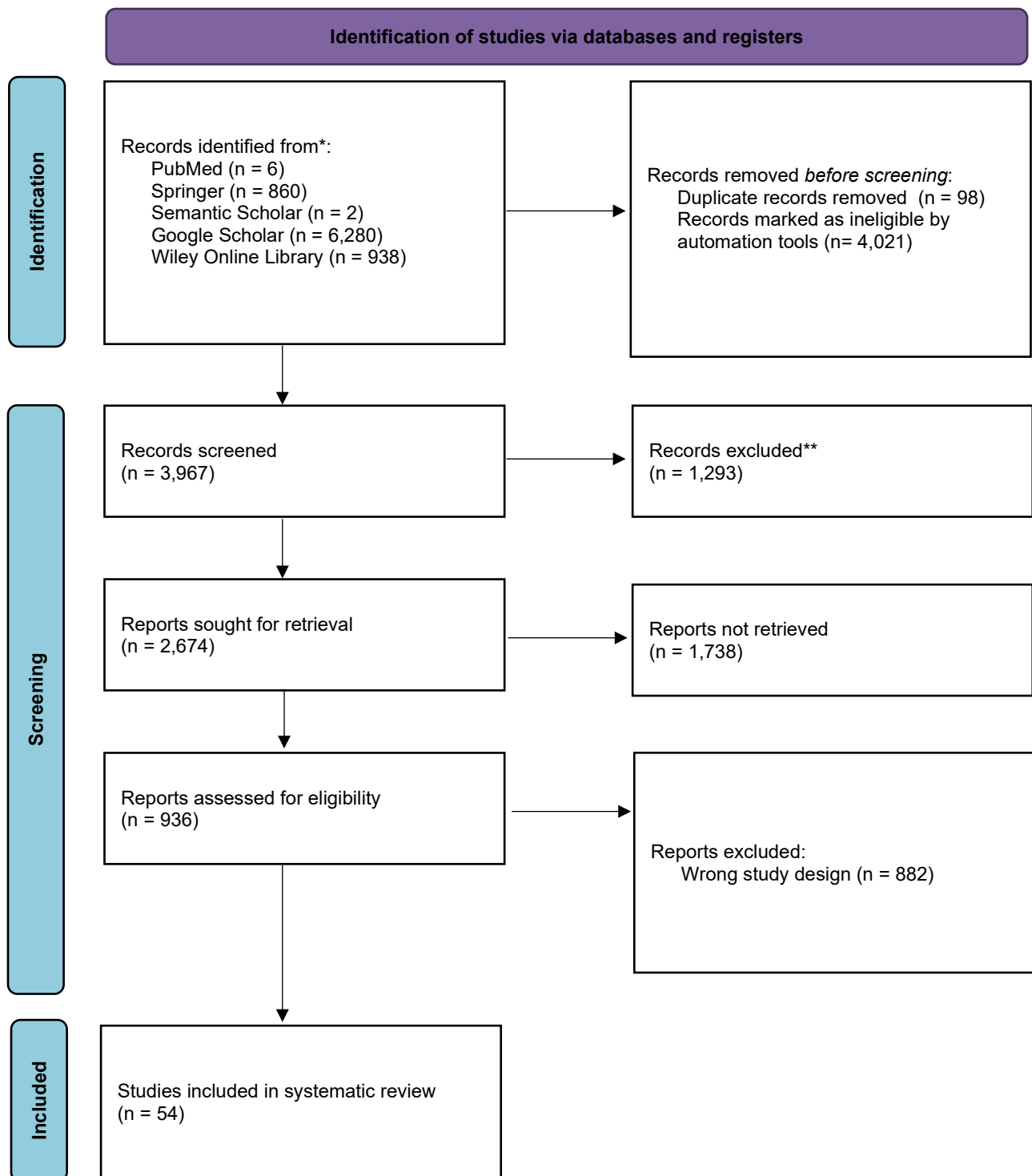


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The 54 included sources encompassed prospective and retrospective cohort studies, etc. The majority focused on systemic sclerosis (SSc) as the primary CTD population, with a smaller subset addressing systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and other CTDs. Right heart catheterization (RHC) served as the diagnostic gold standard for PAH confirmation in most studies, though echocardiographic estimates were used for screening in several.

Study	CTD Population	Primary Focus
H. Gladue et al., 2014	SSc, SLE [2]	Screening and diagnostic modalities for CTD-PAH [2]
A. Young et al., 2019	SSc, SLE [3]	Update on screening measures for CTD-PAH [3]
C. Bruni et al., 2020	SSc [16]	Screening tools for SSc-PAH [16]
V. Smith et al., 2019	SSc (281 patients) [17]	Nailfold videocapillaroscopy in SSc-PAH [17]
Zineb Barkhane et al., 2023	SSc (530 patients) [18]	Mortality predictors in SSc-PAH [18]
S. Johnson et al., 2008	SSc [5]	Prognostic factors for survival in SSc-PAH [5]

Study	CTD Population	Primary Focus
Sarah Madigan et al., 2023	SSc [19]	Exercise tests in screening for SSc-PAH [19]
I. Minopoulou et al., 2021	SSc (101 PAH, 277 no-PAH) [6]	Nailfold capillaroscopy in SSc-PAH [6]
H. Gladue et al., 2013	SSc, SLE, MCTD [20]	Screening and diagnostic modalities in CTD-PAH [20]
B. Dwamena et al., 2009	SSc (220 PAH, 259 controls) [21]	Diagnostic value of BNP/NT-proBNP in SSc-PAH [21]
Yiwen Zhang et al., 2021	SSc (220 PAH, 259 controls) [4]	Diagnostic value of cardiac natriuretic peptide in SSc-PAH [4]
Jieyan Shen et al., 2016	CTD-PAH (n=25), CTD no-PH (n=11) [22]	IVUS for pulmonary vascular assessment in PAH [22]
G. Kovacs et al., 2017	SSc (99 patients) [23]	Changes in pulmonary exercise haemodynamics in SSc [23]
D. Yufang et al., 2025	SLE (273 patients) [24]	Genetic and clinical prediction model for SLE-PAH prognosis [24]
M. Kuwana et al., 2019	CTD (216 patients, 137 SSc) [25]	Risk stratification utility in CTD-PAH treatment [25]

Study	CTD Population	Primary Focus
A. Vanhaecke et al., 2018	SSc [26]	Capillaroscopy and PAH in SSc [26]
P. Xanthouli et al., 2024	SSc (34 patients) [27]	Effect of ambrisentan in SSc with mild PVD [27]
Weizhen Xiang et al., 2022	SSc, SLE, pSS, MCTD, Myositis (6671 patients) [28]	Anti-U1 RNP antibody in CTD-PAH [28]
Yuxuan Jiang et al., 2020	SSc [7]	Risk factors for SSc-PAH [7]
Yuqi Liu et al., 2023	SLE [10]	Risk factors for SLE-PAH [10]
Julie Better et al., 2025	SSc (941 patients from 15 studies) [29]	CPET diagnostic value for SSc-PAH [29]
Song Yang et al., 2019	SSc (1279 patients) [30]	Exercise PASP response in SSc-PAH [30]
Zoe R Brown et al., 2021	SSc [12]	Screening outcomes for SSc-PAH [12]
P. Coral-Alvarado et al., 2008	SSc (349 patients, Colombian) [31]	Risk factors for SSc-PAH in Colombian patients [31]
Jie Wang et al., 2017	SLE [8]	Serological biomarkers for SLE-PAH [8]
Xueping Lun et al., 2023	SLE [11]	Risk factors for SLE-PAH [11]

Study	CTD Population	Primary Focus
D. Khanna et al., 2013	SSc, MCTD, scleroderma-spectrum [32]	Screening recommendations for CTD-PAH [32]
S. Bae et al., 2012	SSc (206 catheterized, mean age 57.2 yr) [33]	Baseline characteristics and outcomes in borderline mPAP [33]
D. Khanna et al., 2013a	SSc, MCTD, scleroderma-spectrum [15]	Screening and detection recommendations for CTD-PAH [15]
S. Zuily et al., 2017	SLE (4480 patients) [9]	Antiphospholipid antibodies and PH risk in SLE [9]
Sunao Miyanaga et al., 2019	CTD (162 patients) [34]	Predictors of exercise-induced PH in CTD [34]
Robert A. Lewis et al., 2020	SSc [35]	BNP/NT-proBNP in PAH diagnosis and risk stratification [35]
T. Kida et al., 2022	SSc (236 patients) [36]	Latent trajectory modeling of PAP in SSc [36]
M. Maeder et al., 2018	PAH general (not CTD-specific) [37]	RV strain imaging in PAH [37]

Study	CTD Population	Primary Focus
G. Murdaca et al., 2016	SSc (69 patients) [14]	Bosentan effect on PAH development in SSc [14]
M. Zhou et al., 2020	Scleroderma (194 patients) [38]	Cardiac evaluation and PH screening in scleroderma [38]
S. Khanna et al., 2023	SSc (2013 patients vs. 1323 controls) [39]	Echocardiographic changes in SSc vs. controls [39]
E. Costa et al., 2020	SSc, SLE (4008 CTD-PAH patients) [40]	Survival in CTD-PAH from registries [40]
C. Iannone et al., 2025	SSc-PH (53 patients) [41]	FVC as survival predictor in SSc-PH [41]
J. Vymětal et al., 2015	SSc (63), MCTD (11) [42]	Echocardiographic and humoral parameters for PH prediction [42]
P. Xanthouli et al., 2024a	SSc (34 patients) [43]	Long-term ambrisentan effect on mild PAH in SSc [43]
P. Xanthouli et al., 2024b	SSc (34 patients) [13]	Long-term ambrisentan follow-up (EDITA- ON) [13]

Study	CTD Population	Primary Focus
J. Bhatt et al., 2020	PAH general (41 patients) [44]	Echocardiographic predictors of early decline in PAH [44]
J. Ai et al., 2019	SSc (298 SSc-PAH) [45]	KCNA5 gene variation and SSc-PAH [45]
G. Laustriat et al., 2016	SSc (1231 patients) [46]	ACPA and SSc clinical presentation [46]
Adla B. Hassan et al., 2023	MCTD (983 patients) [47]	PAH prevalence in MCTD [47]
M. Gegenava et al., 2024	SSc, SLE, pSS (2838 PH, 2656 no-PH) [48]	PH association with outcomes in CTD [48]
Marrietta Theodorakopoulou et al., 2021	SSc (159 participants) [49]	Vascular endothelial injury in SSc-PAH [49]
T. Kramer et al., 2025	PH general (not CTD-specific) [50]	AI applications in PH diagnosis and prognosis [50]
B. Blette et al., 2023	CTD-PAH (776/2503, 31%) [51]	Risk scores as surrogate outcomes in PAH trials [51]

Study	CTD Population	Primary Focus
R. Sagar et al., 2010	SSc-spectrum (57 patients) [52]	Exercise-induced PH hemodynamic subtypes in SSc [52]
D. Khanna et al., 2020	SSc (1485), SLE (456), total CTD-PAH (4008) [1]	Survival in CTD-PAH [1]
Xueping Lun et al., 2023a	SLE [53]	Risk factors for SLE-PH [53]
P. Hendriks et al., 2022	PAH (6999 patients, 97.3% PAH) [54]	Prognostic value of (NT-pro)BNP in PAH [54]

Screening Strategies and Diagnostic Modalities

Echocardiography

Transthoracic echocardiography (TTE) is the most extensively studied screening tool for CTD-PAH. Across three sequential systematic reviews spanning from inception to 2018, echocardiographic parameters were evaluated in the vast majority of included manuscripts [16]. The tricuspid regurgitation velocity (TRV) served as the primary echocardiographic parameter, with screening thresholds ranging from >2.5 m/s (with symptoms) to >3.16 m/s (without symptoms), resulting in 20–67% of patients having RHC-confirmed PAH [2, 20]. Systolic pulmonary arterial pressure (sPAP) was reported in 22 of 32 papers in one systematic review, with 40 mmHg being the most frequently used cut-off [16]. The sensitivity of TTE ranged from 49% to 95%, with specificity from 43% to 100%, depending on the threshold applied [2].

A meta-analysis of 37 studies comparing SSc patients with healthy controls found that pulmonary artery systolic pressure demonstrated the highest overall effect size among echocardiographic parameters (SMD 0.97; 95% CI 0.63–1.31; $p < 0.01$), followed by LV global longitudinal strain (SMD 0.94; 95% CI 0.55–1.31; $p < 0.01$) and TAPSE (SMD 0.43; 95% CI 0.19–

0.68; $p < 0.01$) [39]. Additional echocardiographic parameters including right atrial volume index, left ventricular eccentricity index, estimated PASP, and right ventricular basal dimension were significant predictors of clinical decline in a case-control study of PAH patients [44]. Right ventricular free wall strain by speckle tracking and fractional area change (FAC) also showed significant correlations with pulmonary artery systolic pressure in SSc and MCTD patients [42].

Latent trajectory modeling applied to repeated sPAP measurements in 236 SSc patients identified five distinct patterns of pulmonary pressure elevation: rapid progression (3.8%), early elevation (12.7%), mid elevation (22.9%), late elevation (10.2%), and low stable (50.4%) [36]. Cardiac involvement was associated with rapid progression (adjusted OR 28.9, 95% CI 3.21–259.5), diffuse cutaneous SSc with early elevation (OR 4.08, 95% CI 1.27–13.1), and anti-centromere antibody positivity with mid elevation (OR 4.50, 95% CI 1.11–18.2) [36].

Pulmonary Function Tests

Pulmonary function tests (PFTs), particularly diffusing capacity for carbon monoxide (DLCO), are integral to PAH screening. A low DLCO (45–70% predicted) was associated with a 5.6–7.4% development of PAH, and declining DLCO increased specificity for PAH detection: DLCO $\leq 60\%$ predicted yielded a specificity of 45%, while DLCO $\leq 50\%$ predicted reached a specificity of 90% [2, 20]. The FVC/DLCO ratio, when combined with TRV, resulted in greater sensitivity and negative predictive value (NPV) compared to TRV alone [3]. Consensus recommendations specified that DLCO $< 60\%$ predicted and disease duration > 3 years should trigger use of the DETECT algorithm [15, 32].

Baseline forced vital capacity (FVC) $< 70\%$ was identified as a major independent negative prognostic factor in SSc-PH patients (OR 68.3 for mortality in PH-ILD patients with FVC $< 70\%$, 95% CI 2.28–145, $p = 0.01$), with an AUC of 0.713 (95% CI 0.564–0.861) for predicting death [41]. Five-year survival rates differed dramatically: 88% for PAH without ILD, 67% for PH-ILD with FVC $\geq 70\%$, and only 29% for PH-ILD with FVC $< 70\%$ [41].

Biomarkers

NT-proBNP and BNP. Multiple systematic reviews and meta-analyses confirmed the diagnostic utility of natriuretic peptides. A pooled meta-analysis of 9 studies (220 SSc-PAH

patients, 259 controls) reported a sensitivity of 0.67 (95% CI 0.52–0.79) and specificity of 0.84 (95% CI 0.75–0.91) for BNP/NT-proBNP in diagnosing SSc-PAH [4, 21]. Earlier systematic reviews reported higher sensitivity (90–100%) for NT-proBNP at a cut-off >239 pg/ml, with specificity ranging from 45–95% [2, 20]. In one SSc screening study, NT-proBNP >395 ng/L had a positive predictive value of 95.1% but a sensitivity of only 55.9% [35]. The prognostic value of natriuretic peptides was confirmed in a meta-analysis of 16 studies (6999 PAH patients), where elevated NT-proBNP and BNP conferred pooled hazard ratios for mortality of 2.75 (95% CI 1.86–4.07) and 3.87 (95% CI 2.69–5.57), respectively [54]. In scleroderma patients, BNP >100 pg/ml predicted PH probability with 52.9% sensitivity and 88.2% specificity [38].

Autoantibodies. Anti-U1 RNP antibody was a significant risk factor for PAH among CTD patients (OR 5.30, 95% CI 2.96–9.48) and was simultaneously a protective factor against mortality in CTD-PAH patients (HR 0.55, 95% CI 0.36–0.83) [28]. In SLE specifically, anti-RNP antibody carried an odds ratio of 3.68 (95% CI 2.04–6.63) for PAH, and anti-Sm antibody an OR of 1.71 (95% CI 1.06–2.76) [8]. Antiphospholipid antibodies identified SLE patients at risk of PH with a pooled OR of 2.28 (95% CI 1.65–3.15) [9]. Anti-citrullinated protein antibodies (ACPA) in SSc were associated with PAH with an OR of 7.72 (95% CI 2.38–25.5) [46]. Anti-centromere antibodies were identified as a frequent association with SSc-PAH in multiple studies [7, 16].

Composite Screening Algorithms

Composite algorithms consistently outperformed single-modality screening. The DETECT algorithm achieved 96–100% sensitivity and 100% NPV in different SSc cohorts, though specificity was lower (48%) [2, 3]. The Australian Scleroderma Interest Group (ASIG) algorithm similarly demonstrated 94% sensitivity and 87% NPV [3]. Both DETECT and ASIG had greater sensitivity and NPV compared to the 2009 ESC/ERS guidelines [3, 16]. Consensus recommendations endorsed initial screening with TTE, PFTs (including DLCO), and NT-proBNP for all SSc and scleroderma-spectrum disorder patients, with annual TTE and PFTs and full panels upon new symptoms [15, 32].

Exercise Testing

Exercise-based screening modalities were assessed in several studies. A systematic review of eight studies found that exercise tests (CPET, six-minute walk test, stress Doppler echocardiography) predicted PAH with sensitivity of 50–100% and specificity of 73–91% [19]. A meta-analysis of 12 studies (1279 SSc patients) demonstrated that the difference between rest and post-exercise PASP (Δ PASP) was significantly elevated in PAH patients (pooled mean 36.2 mmHg, 95% CI 29.7–42.7) compared to non-PAH SSc patients (12.2 mmHg, 95% CI 11.2–13.2), with a proposed cut-off of Δ PASP >29 mmHg for high suspicion of PAH [30]. A prospective cohort of 99 scleroderma patients followed for approximately 4 years showed that sPAP at 50W exercise (sPAP50) increased significantly ($p < 0.001$), while resting sPAP was unchanged ($p = 0.38$), confirming that exercise hemodynamics may reveal early pulmonary vascular disease [23]. CPET-derived VE/VCO₂ at ventilatory threshold was significantly higher in SSc-PAH versus SSc without PAH (39.81 vs. 32.68), with a mean effect size of -1.182 (95% CI -1.691 to -0.672 ; $p < 0.001$) [29]. Resting mPAP ≥ 14 mmHg combined with PVR ≥ 160 dynes/sec/cm⁻⁵ predicted exercise-induced PH with a positive predictive value of 89–100% [52].

Nailfold Capillaroscopy

Two systematic reviews and one meta-analysis evaluated nailfold videocapillaroscopy (NVC) in SSc-PAH. Capillary density was reduced in SSc-PAH patients (WMD -1.2 , 95% CI -2.3 to -0.1 when confirmed by RHC), and capillary loop width was increased (WMD 10.9 , 95% CI 2.5 – 19.4) [6]. SSc-PAH patients had a 7.3-fold higher likelihood of active or late scleroderma pattern (95% CI 3.0 – 18.0) [6]. Longitudinal studies demonstrated that progressive capillary loss ($p = 0.04$ and $p = 0.033$) and worsening NVC pattern (HR 5.12 , 95% CI 1.23 – 21.27) predicted incident PAH [17]. These findings were corroborated by a second systematic review identifying avascular score, morphology changes, and scleroderma pattern severity as cross-sectionally associated with PAH [26].

Artificial Intelligence Approaches

A systematic review of 53 studies on AI in PH found that machine learning and deep learning models achieved AUC values of 0.71–1.00 for PH diagnosis and prognosis, using clinical,

echocardiographic, imaging, or molecular data [50]. However, most were retrospective single-center studies with limited external validation, and only 15 studies used RHC for diagnostic confirmation [50]. Applicability to CTD-specific populations was not explicitly addressed [50].

Risk Factors for PAH Development

Risk Factors in Systemic Sclerosis

The following table summarizes identified risk factors for PAH development in SSc patients:

Risk Factor Category	Specific Factors	Effect Estimate
Demographic	Older age	Frequently identified association [7]
Demographic	Male gender	HR 1.67 (95% CI 1.15–2.44), p=0.008 [18]
Clinical	Telangiectasias	Frequent association [7, 16]
Clinical	Dyspnea (unexplained)	Reported in 9/15 papers with clinical parameters [16]
Clinical	Pulmonary fibrosis	AOR 7.37 (95% CI 3.67–14.81) [31]
Clinical	Microstomia	AOR 3.3 (95% CI 1.70–6.28) [31]
Clinical	GI manifestations	AOR 2.41–2.7 [31]
Clinical	Pericardial effusion	HR 1.73 (95% CI 1.21–2.48) [18]
Clinical	Cardiac involvement	OR 28.9 (95% CI 3.21–259.5) for rapid PAP trajectory [36]

Risk Factor Category	Specific Factors	Effect Estimate
Pulmonary function	Low DLCO (45–70% predicted)	5.6–7.4% PAH development rate [2]
Pulmonary function	FVC <70%	OR 68.3 for mortality (95% CI 2.28–145) [41]
Hemodynamic	Initial sPAP >60 mmHg	HR 3.60 (95% CI 1.42–9.15) [5]
Hemodynamic	Elevated mRAP	HR 20.7, p=0.0001 [5]
Hemodynamic	Borderline mPAP (21–24 mmHg)	55% developed resting PH over 25.7 months [33]
Biomarker	NT-proBNP elevated	Sensitivity 90–100% at >239 pg/ml [2]
Biomarker	BNP >100 pg/ml	Sens 52.9%, Spec 88.2% [38]
Autoantibody	Anti-centromere antibody	Frequent association (4 studies) [7]
Autoantibody	ACPA positivity	OR 7.72 (95% CI 2.38–25.5) [46]
Genetic	HLA-DRw6	RR 54.52, p=0.01 [5]
Genetic	HLA-DRw52	p=0.02 [5]
Genetic	KCNA5 rs10744676	Not confirmed (OR 0.51–0.64, p=NS) [45]

Risk Factor Category	Specific Factors	Effect Estimate
SSc subtype	Diffuse cutaneous SSc	OR 4.08 for early PAP elevation trajectory [36]
Microvascular	Reduced capillary density	WMD -1.2 (95% CI -2.3 to -0.1) [6]
Microvascular	Active/late NVC pattern	OR 7.3 (95% CI 3.0–18.0) [6]
Temporal	Shorter SSc onset to PAH interval	5.24 vs. 9.93 years, p<0.01 [5]
Temporal	Disease duration >3 years	Trigger for DETECT algorithm [32]
Anemia	Anemia	AOR 5.4 (95% CI 1.98–14.93) [31]

A systematic review of 37 eligible articles identified 43 distinct factors for SSc-PAH across seven categories, with patient characteristics (14 factors), pulmonary physiology (6), antibody profiles (6), and genetics/epigenetics (6) harboring the most numerous and diverse factors [7]. Low DLCO (6 studies), older age (4 studies), longer disease duration (4 studies), positive anticentromere antibodies (4 studies), telangiectasias (4 studies), and high BNP (4 studies) were the most frequently identified associations [7].

Risk Factors in Systemic Lupus Erythematosus

Risk Factor	Effect Estimate
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Risk Factor	Effect Estimate
Raynaud's phenomenon	RR 1.83 (95% CI 1.41–2.37) [10]; OR 2.39 (95% CI 1.91–2.99) [11]
Interstitial lung disease	RR 4.36 (95% CI 2.42–7.85) [10]; OR 3.28 (95% CI 2.37–4.53) [11]
Pericardial effusion	RR 3.33 (95% CI 2.20–5.05) [10]; OR 2.97 (95% CI 2.37–3.72) [11]
Serositis	RR 2.29 (95% CI 1.89–2.77) [10]; OR 2.28 (95% CI 1.83–2.84) [11]
Anti-RNP antibody	OR 3.68 (95% CI 2.04–6.63) [8]; OR 1.77 (95% CI 1.17–2.65) [11]
Anti-Sm antibody	OR 1.71 (95% CI 1.06–2.76) [8]
Anti-U1 RNP antibody	OR 5.30 (95% CI 2.96–9.48) [28]; RR 1.58 (95% CI 1.07–2.34) [10]
Antiphospholipid antibodies	OR 2.28 (95% CI 1.65–3.15) [9]
Anti-SSA	RR 1.28 (95% CI 1.01–1.62) [10]
Anti-SSB	RR 1.38 (95% CI 1.19–1.60) [10]
Rheumatoid factor	OR 1.66 (95% CI 1.24–2.24) [11]

Risk Factor	Effect Estimate
Vasculitis	OR 1.50 (95% CI 1.08–2.07) [11]
Thrombocytopenia	RR 1.38 (95% CI 1.14–1.68) [10]
Female gender	RR 1.04 (95% CI 1.02–1.06) [10]
Current smoking	RR 2.20 (95% CI 1.19–4.06) [10]
Systemic hypertension	RR 1.30 (95% CI 1.07–1.58) [10]

Raynaud's phenomenon, interstitial lung disease, pericardial effusion, serositis, and anti-RNP antibodies were consistently identified across multiple independent meta-analyses as significant risk factors for SLE-PAH [8, 10, 11]. The SLE autoantibody profile contrasts with SSc in that anti-RNP and anti-Sm antibodies are prominent risk factors, reflecting the distinct immunological pathways in SLE-associated pulmonary vascular disease.

Risk Factors in Mixed Connective Tissue Disease

A meta-analysis of eight studies (983 patients) found a pooled PAH prevalence of 12.53% (95% CI 8.30–18.48%) in MCTD, with significant heterogeneity ($I^2 = 83.3\%$) [47]. No association was found between PAH and female gender or age in MCTD [47]. Consensus recommendations suggested that MCTD patients with scleroderma features should undergo screening identical to SSc patients [15, 32].

Prognostic Factors and Survival Outcomes

Survival in CTD-PAH

A meta-analysis of 19 registries (4008 CTD-PAH patients) reported 1-, 2-, and 3-year survival rates of 83%, 73%, and 62%, respectively, which were lower than the overall PAH population (88%, 79%, 72%) [1, 40]. SSc-PAH patients had worse survival than SLE-PAH patients: 88% vs. 92% at 1 year, 75% vs. 90% at 2 years, and 67% vs. 87% at 3 years [1]. CTD-PAH patients

treated from 2010 onward showed numerically higher survival rates than those treated earlier (90% vs. 85% at 1 year, 82% vs. 74% at 2 years, 73% vs. 65% at 3 years) [1], potentially reflecting increased screening and newer treatment approaches. The meta-analysis by Gegenava et al. confirmed significantly worse survival in SSc-PH compared to SSc without PH (OR 3.70, 95% CI 2.42–5.67; $p < 0.00001$) and compared to other causes of PH including SLE (OR 2.76, 95% CI 1.95–3.91; $p < 0.00001$) [48].

In SSc-PAH specifically, pooled 1-, 3-, and 5-year survival rates were 90% (95% CI 86–93%), 66% (95% CI 59–72%), and 44% (95% CI 23–65%), respectively [18]. Independent mortality predictors included age (HR 1.02, $p = 0.02$), male gender (HR 1.67, $p = 0.008$), pericardial effusion (HR 1.73, $p = 0.003$), cardiac index (HR 0.51, $p = 0.0001$), six-minute walk distance (HR 0.98, $p = 0.04$), pulmonary arterial pressure (HR 1.03, $p = 0.01$), and NYHA classification (HR 3.26, $p = 0.0002$) [18].

Genetic Risk and Prognosis in SLE-PAH

In a prospective cohort of 273 SLE-PAH patients, a genetic risk score (GRS) based on 112 non-HLA loci was positively correlated with mortality (HR 6.82, 95% CI 2.12–21.91, $p = 0.001$) [24]. The AUC for GRS alone was 0.713, while combining GRS with a clinical prognostic index improved the AUC to 0.849 (vs. 0.73 for clinical index alone) [24]. Survival rates stratified by combined risk were 97.65% for clinical low-risk, 92.98% for clinical high-risk with low GRS, and 76.09% for clinical high-risk with high GRS [24].

Risk Stratification in Treatment

A post-hoc analysis of the AMBITION trial (216 CTD-PAH patients) demonstrated that a simplified risk stratification using 6-minute walk distance, NT-proBNP, and WHO-FC at baseline and week 16 predicted outcomes [25]. Combination therapy (ambrisentan plus tadalafil) reduced clinical failure risk compared to monotherapy in the baseline intermediate risk group (HR 0.519, 95% CI 0.297–0.905, $p = 0.02$) and in the week-16 low risk group (HR 0.069, 95% CI 0.009–0.548, $p < 0.001$) [25]. However, an individual participant data meta-analysis of three large PAH RCTs (AMBITION, GRIPHON, SERAPHIN; $n = 2508$) found that attainment of low-risk status by 16

weeks explained only 7–13% of treatment effects on long-term clinical worsening, indicating that current multicomponent risk scores may not serve as adequate surrogate endpoints [51].

Benefits of Screening Programs

A systematic review and meta-analysis of long-term screening outcomes demonstrated improved survival in SSc-PAH patients diagnosed through screening programs compared to those diagnosed clinically [12]. Screened populations had better risk stratification parameters at PAH diagnosis, including more favorable functional class and hemodynamic profiles, though not all differences reached statistical significance [12]. This supports the rationale for annual screening in asymptomatic SSc patients [12].

Early treatment with ambrisentan in SSc patients with mild pulmonary vascular disease (mPAP borderline but not meeting full PAH criteria) demonstrated significant hemodynamic benefit. In the EDITA-ON follow-up study, ambrisentan-treated patients showed mPAP improvement (-1.53 ± 2.53 mmHg) compared to worsening in untreated controls ($+1.91 \pm 2.98$ mmHg, $p=0.003$) [13]. No ambrisentan-treated patient developed PAH, while 4–6 of 12–15 untreated patients progressed to PAH ($p<0.0001$) [13, 27]. Separately, long-term bosentan treatment in SSc patients with digital ulcers prevented PAH development (0/25 treated vs. 7/44 controls), with a significant decline in mean sPAP from 33.64 to 26.20 mmHg in the treatment group versus an increase from 33.57 to 39.41 mmHg in controls [14].

Synthesis

The most consistent finding across this body of evidence is the superiority of composite, multi-modal screening approaches over any single screening modality for detecting PAH in CTD patients. Individually, TTE provides moderate sensitivity (49–95%) but variable specificity depending on threshold, DLCO offers high specificity at lower cut-offs but limited sensitivity, and NT-proBNP provides moderate sensitivity with good specificity [2, 20, 21]. The DETECT and ASIG algorithms, which integrate echocardiographic, biomarker, and pulmonary function data, achieve near-perfect sensitivity (96–100%) and NPV (87–100%) at the cost of lower specificity and high referral rates for RHC [2, 3].

The heterogeneity in reported screening performance largely reflects differences in threshold selection. Higher TRV cut-offs (>3.0 m/s) yield greater specificity but miss patients with early-stage disease, while lower thresholds (>2.5 m/s with symptoms) capture more cases at the cost of more false positives [2]. Similarly, lower DLCO thresholds ($\leq 50\%$ predicted) achieve 90% specificity but miss patients with moderately reduced diffusion capacity [2]. The DETECT algorithm resolves this by weighting multiple parameters, thereby reducing the false-negative rate that matters most in a disease with high mortality if undetected.

Risk factor profiles differ meaningfully between SSc-PAH and SLE-PAH. In SSc, the dominant predictors are hemodynamic (sPAP, mRAP), functional (DLCO, 6-minute walk distance), and microvascular (capillary density, NVC pattern), reflecting the progressive vasculopathy that characterizes SSc pulmonary vascular disease [2, 6, 7]. In SLE, autoantibody profiles (anti-RNP, anti-Sm, antiphospholipid) and clinical features of systemic inflammation (serositis, pericardial effusion, Raynaud's) predominate [8–10], consistent with the inflammatory and thrombotic mechanisms underlying SLE-PAH. The paradoxical finding that anti-U1 RNP antibody is both a risk factor for PAH development (OR 5.30) and a protective factor against PAH-related mortality (HR 0.55) [28] likely reflects that anti-U1 RNP-positive CTD-PAH may be more responsive to immunosuppressive therapy, a known treatment advantage in SLE-PAH and MCTD-PAH.

The observation that SSc-PAH carries worse survival than SLE-PAH (67% vs. 87% at 3 years) [1] is consistent across multiple registries and likely reflects the progressive, fibroproliferative vasculopathy in SSc that is less amenable to vasodilator therapy alone, compared to the reversible inflammatory component in SLE-PAH. The improving survival trends in CTD-PAH over time [1] coincide with the implementation of screening programs [12] and the availability of combination therapy [25], though these temporal associations cannot establish causality from registry data.

The evidence for exercise testing and nailfold capillaroscopy as complementary screening modalities is promising but based on smaller studies with significant heterogeneity ($I^2 = 70\text{--}86\%$ for capillaroscopy parameters) [6]. Exercise echocardiography detects hemodynamic abnormalities that resting studies miss — a finding confirmed by the prospective 4-year follow-up showing significant

deterioration in exercise but not resting pulmonary pressures [23] — but standardization of exercise protocols and cut-offs remains a barrier to widespread adoption [19].

The current evidence is overwhelmingly centered on SSc, with limited data for SLE, MCTD, and other CTDs. Consensus recommendations explicitly state that screening of asymptomatic patients is not recommended for CTDs without scleroderma features [15], reflecting the sparse evidence base. For SLE, the identification of aPL, anti-RNP, and anti-Sm as risk factors suggests that targeted screening in antibody-positive patients with relevant clinical features (Raynaud's, serositis, ILD) would be most efficient [8, 10]. The integration of genetic risk scores with clinical models, as demonstrated in the CSTAR-PAH cohort for SLE-PAH (AUC improvement from 0.73 to 0.849) [24], represents an emerging approach that may further refine risk stratification but requires validation in independent cohorts.

The evidence for early treatment of borderline or mild pulmonary vascular disease is based on small single-center studies (n=34–69) [13, 14], limiting generalizability. Nevertheless, the consistent direction of effect — ambrisentan preventing PAH development in SSc patients with borderline hemodynamics [13] and bosentan preventing PAH in SSc patients with digital ulcers [14] — supports the clinical rationale for early identification and treatment of at-risk patients.

DISCUSSION

This systematic review synthesizes evidence from 54 studies investigating risk factors and screening strategies for PAH in patients with connective tissue diseases, providing several important insights that advance our understanding of CTD-PAH prediction and have direct implications for clinical practice.

Superiority of Multi-Modal Screening Approaches

The most consistent and robust finding across this body of evidence is the clear superiority of composite, multi-modal screening algorithms over any single screening modality for detecting PAH in CTD patients. The DETECT and ASIG algorithms, which integrate echocardiographic parameters, pulmonary function tests, and biomarker data, achieved near-perfect sensitivity (94-100%) and negative predictive value (87-100%) across multiple validation cohorts [2, 3, 16]. This

performance represents a substantial improvement over the 2009 ESC/ERS guidelines, which demonstrated significantly lower sensitivity and would have missed a considerable proportion of PAH cases [3, 16].

The explanation for this superiority lies in the complementary nature of the individual screening components. Transthoracic echocardiography, while providing direct hemodynamic assessment, exhibits threshold-dependent performance characteristics. Higher TRV cut-offs (>3.0 m/s) yield excellent specificity but fail to identify patients with early-stage disease, whereas lower thresholds (>2.5 m/s with symptoms) capture more cases at the cost of increased false-positive referrals for right heart catheterization [2, 20]. Similarly, DLCO offers high specificity (90%) at lower cut-offs ($\leq 50\%$ predicted) but limited sensitivity, while NT-proBNP provides moderate sensitivity with good specificity [2, 21]. The DETECT algorithm resolves this trade-off by weighting multiple parameters simultaneously, thereby reducing the false-negative rate that matters most in a disease where delayed diagnosis carries grave consequences [12].

The clinical implications are clear: annual screening of asymptomatic SSc patients using composite algorithms should be considered the standard of care. This recommendation is reinforced by meta-analytic evidence demonstrating improved survival in patients diagnosed through screening programs compared to those diagnosed clinically, with screened populations exhibiting more favorable functional class and hemodynamic profiles at diagnosis [12]. The observation that survival in CTD-PAH has improved over time, coinciding with the implementation of screening programs and availability of combination therapy, further supports this approach [1, 25].

CTD-Specific Risk Factor Profiles

A major finding of this review is the substantial heterogeneity in risk factor profiles between different CTD subtypes, which has important implications for pathophysiology and screening strategies. In SSc, the dominant predictors reflect progressive vasculopathy and fibroproliferative disease: hemodynamic parameters (sPAP, mRAP), functional measures (DLCO, six-minute walk distance), and microvascular abnormalities (capillary density, nailfold capillaroscopy patterns) [2, 6, 7]. The identification of distinct trajectories of pulmonary pressure elevation in SSc—rapid progression, early elevation, mid elevation, late elevation, and low stable—further emphasizes the

heterogeneous nature of SSc-PAH and suggests that risk stratification may need to account for individual disease trajectories [36].

In contrast, SLE-PAH risk factors are dominated by autoantibody profiles and clinical features of systemic inflammation. Anti-RNP antibody (OR 3.68), anti-Sm antibody (OR 1.71), and antiphospholipid antibodies (OR 2.28) emerged as significant predictors, along with clinical manifestations including Raynaud's phenomenon, serositis, pericardial effusion, and interstitial lung disease [8-11]. This profile is consistent with inflammatory and thrombotic mechanisms underlying SLE-PAH, distinguishing it from the fibroproliferative vasculopathy of SSc. The paradoxical finding that anti-U1 RNP antibody serves both as a risk factor for PAH development (OR 5.30) and a protective factor against PAH-related mortality (HR 0.55) likely reflects the greater responsiveness of anti-U1 RNP-positive disease to immunosuppressive therapy, a recognized treatment advantage in SLE-PAH and MCTD-PAH [28].

For MCTD, the pooled PAH prevalence of 12.53% (95% CI 8.30-18.48%) is comparable to SSc, but the evidence base remains limited [47]. Consensus recommendations that MCTD patients with scleroderma features should undergo screening identical to SSc patients represent a pragmatic approach pending more robust data [15, 32].

These CTD-specific risk profiles have direct clinical implications. For SSc, comprehensive annual screening using composite algorithms is warranted for all patients, with particular attention to those with low DLCO, anti-centromere antibodies, telangiectasias, and nailfold capillaroscopic abnormalities. For SLE, a more targeted approach may be appropriate, focusing screening efforts on patients with high-risk autoantibody profiles (anti-RNP, anti-Sm, antiphospholipid antibodies) and relevant clinical features (Raynaud's phenomenon, serositis, pericardial effusion, interstitial lung disease). This targeted strategy would optimize resource utilization while maintaining sensitivity for detecting PAH in high-risk subsets.

Prognostic Factors and Survival Disparities

The consistent observation that SSc-PAH carries worse survival than SLE-PAH (67% vs. 87% at 3 years) across multiple international registries warrants careful consideration [1, 40, 48]. This disparity likely reflects fundamental differences in underlying pathophysiology: the

progressive, fibroproliferative vasculopathy in SSc is less amenable to vasodilator therapy alone, whereas the reversible inflammatory component in SLE-PAH may respond more favorably to immunosuppressive and immunomodulatory approaches [28]. The identification of forced vital capacity <70% as a major independent negative prognostic factor in SSc-PH patients (OR 68.3 for mortality) underscores the importance of concomitant interstitial lung disease in determining outcomes [41].

The improving survival trends in CTD-PAH over time—90% vs. 85% at 1 year, 82% vs. 74% at 2 years, and 73% vs. 65% at 3 years for patients treated from 2010 onward compared to earlier eras—are encouraging [1]. While these temporal associations cannot establish causality from registry data, they coincide with the implementation of systematic screening programs [12], increased awareness of CTD-PAH, and the availability of combination therapy regimens [25]. The post-hoc analysis of the AMBITION trial demonstrating that combination therapy (ambrisentan plus tadalafil) reduced clinical failure risk compared to monotherapy in intermediate-risk patients provides supportive evidence for contemporary treatment approaches [25].

Emerging Screening Modalities

Several emerging screening modalities show promise for enhancing early detection of CTD-PAH. Exercise testing, including cardiopulmonary exercise testing, six-minute walk test, and stress Doppler echocardiography, detects hemodynamic abnormalities that resting studies miss—a finding confirmed by prospective 4-year follow-up showing significant deterioration in exercise but not resting pulmonary pressures [23]. The pooled mean difference in Δ PASP between PAH and non-PAH SSc patients (36.2 mmHg vs. 12.2 mmHg) and the proposed cut-off of Δ PASP >29 mmHg for high suspicion of PAH provide quantitative benchmarks for clinical application [30]. However, standardization of exercise protocols and cut-offs remains a barrier to widespread adoption [19].

Nailfold videocapillaroscopy represents another promising adjunctive tool, with meta-analytic evidence demonstrating reduced capillary density (WMD -1.2, 95% CI -2.3 to -0.1) and increased capillary loop width (WMD 10.9, 95% CI 2.5-19.4) in SSc-PAH patients [6]. The 7.3-fold higher likelihood of active or late scleroderma pattern in SSc-PAH patients and the demonstration that progressive capillary loss predicts incident PAH suggest that capillaroscopy may identify

patients at particularly high risk [6, 17]. Integration of capillaroscopic findings into multi-modal screening algorithms could potentially enhance risk stratification, though prospective validation is needed.

The integration of genetic risk scores with clinical prediction models, as demonstrated in the CSTAR-PAH cohort for SLE-PAH (AUC improvement from 0.73 to 0.849), represents an exciting frontier [24]. The finding that a genetic risk score based on 112 non-HLA loci was positively correlated with mortality (HR 6.82) and that combining genetic and clinical data improved risk discrimination suggests that genomic information may eventually contribute to personalized risk stratification. Similarly, artificial intelligence approaches achieving AUC values of 0.71-1.00 for PH diagnosis and prognosis using clinical, echocardiographic, and molecular data hold promise, though current limitations including retrospective design, single-center derivation, and limited external validation temper immediate clinical applicability [50].

Evidence Gaps and Future Directions

Despite the substantial body of evidence synthesized in this review, several critical gaps remain. The overwhelming predominance of SSc-focused research (38 of 54 studies) leaves uncertainty regarding optimal screening strategies for SLE, MCTD, and other CTDs. Consensus recommendations explicitly state that screening of asymptomatic patients is not recommended for CTDs without scleroderma features, reflecting this sparse evidence base [15]. Large-scale, prospective cohort studies in non-scleroderma CTD populations are urgently needed.

The evidence for early treatment of borderline or mild pulmonary vascular disease, while promising, is based on small single-center studies with limited sample sizes (n=34-69) [13, 14, 27]. The consistent direction of effect—ambrisentan preventing PAH development in SSc patients with borderline hemodynamics and bosentan preventing PAH in SSc patients with digital ulcers—supports the clinical rationale for early intervention but requires confirmation in adequately powered multicenter trials. The EDITA-ON follow-up study's finding that no ambrisentan-treated patient developed PAH compared to 4-6 of 12-15 untreated controls ($p<0.0001$) is compelling but requires replication [13].

The observation that attainment of low-risk status by 16 weeks explains only 7-13% of treatment effects on long-term clinical worsening in large RCTs [51] raises important questions about the adequacy of current multicomponent risk scores as surrogate endpoints. This finding suggests that more refined risk stratification tools, potentially incorporating novel biomarkers, genetic information, and imaging parameters, may be needed to accurately capture treatment effects and guide therapeutic decisions.

Standardization of screening protocols, including echocardiographic parameters, exercise testing procedures, and biomarker cut-offs, remains an unmet need. The heterogeneity in reported screening performance across studies largely reflects differences in threshold selection rather than true variability in test characteristics [2, 16]. Development and validation of standardized protocols would facilitate comparison across studies and enable development of evidence-based guidelines.

Clinical Implications

Despite these limitations, several clinical recommendations can be derived from this systematic review. For SSc patients, annual screening using composite algorithms incorporating echocardiography, pulmonary function tests (including DLCO), and NT-proBNP should be standard practice. The DETECT algorithm is recommended for patients with disease duration >3 years and DLCO <60% predicted. For SLE patients, targeted screening should be considered in those with high-risk autoantibody profiles (anti-RNP, anti-Sm, antiphospholipid antibodies) and relevant clinical features (Raynaud's phenomenon, serositis, pericardial effusion, interstitial lung disease). For MCTD patients with scleroderma features, screening analogous to SSc is reasonable. Patients with borderline hemodynamics or exercise-induced pulmonary hypertension should be considered for closer monitoring and potentially for clinical trials of early intervention.

CONCLUSION AND RECOMMENDATIONS

This systematic review provides a comprehensive synthesis of the current evidence on risk factors and screening strategies for pulmonary arterial hypertension in patients with connective tissue diseases. The findings demonstrate that composite, multi-modal screening algorithms significantly outperform single-modality approaches, achieving near-perfect sensitivity and

negative predictive value for PAH detection in SSc populations. Risk factor profiles differ substantially between CTD subtypes, reflecting distinct underlying pathophysiological mechanisms: SSc-PAH is characterized by progressive vasculopathy with hemodynamic, functional, and microvascular predictors, while SLE-PAH is dominated by autoantibody profiles and inflammatory clinical features. Survival outcomes are consistently worse in SSc-PAH compared to SLE-PAH, highlighting the need for CTD-specific therapeutic approaches.

The evidence supporting screening programs is robust for SSc, with demonstrated improvements in early detection and survival. For other CTD subtypes, targeted screening based on identified risk factor profiles represents a pragmatic approach pending further research. Emerging modalities including exercise testing, nailfold capillaroscopy, and genetic risk stratification show promise for enhancing early detection and risk prediction but require standardization and prospective validation.

Recommendations for Clinical Practice

1. All patients with SSc should undergo annual PAH screening using composite algorithms incorporating echocardiography, pulmonary function tests (including DLCO), and NT-proBNP.
2. The DETECT algorithm should be applied in SSc patients with disease duration >3 years and DLCO <60% predicted.
3. SLE patients with high-risk autoantibody profiles (anti-RNP, anti-Sm, antiphospholipid antibodies) and relevant clinical features (Raynaud's phenomenon, serositis, pericardial effusion, interstitial lung disease) should be considered for targeted PAH screening.
4. MCTD patients with scleroderma features should undergo screening analogous to SSc patients.
5. Patients with borderline hemodynamics or exercise-induced pulmonary hypertension warrant close monitoring and consideration for clinical trials of early intervention.

Recommendations for Future Research

1. Large-scale, prospective cohort studies in non-scleroderma CTD populations are urgently needed to establish evidence-based screening recommendations.
2. Validation studies of emerging modalities including exercise testing, nailfold capillaroscopy, and genetic risk scores should be prioritized.
3. Multicenter randomized controlled trials of early intervention in patients with borderline hemodynamics or high-risk features are required to determine whether treatment prevents or delays progression to overt PAH.
4. Development and validation of standardized screening protocols would facilitate comparison across studies and enable evidence-based guideline development.
5. Integration of novel biomarkers, imaging parameters, and genetic information into refined risk prediction models may improve risk stratification and guide personalized screening and treatment approaches.

In conclusion, while substantial progress has been made in understanding and detecting CTD-PAH, continued research efforts are needed to optimize screening strategies, validate emerging technologies, and develop CTD-specific therapeutic approaches that can improve the poor prognosis associated with this devastating complication.

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