Review

The prevalence of pulmonary arterial hypertension in patients with mixed connective tissue disease: a systematic review and meta-analysis

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ABSTRACT

Objective. *The prevalence and outcome of mixed connective tissue disease-associated pulmonary arterial hypertension (MCTD-PAH) has not been well understood. Our aim was to review the current knowledge on the prevalence, severity, and mortality of MCTD-PAH. We also aimed to examine the prevalence trend of MCTD-PAH over the years.*

Methods. *PubMed/Medline, Embase, Scopus and Web of Science electronic databases were searched for the published randomised controlled clinical trials (RCTs) and observational/original studies on PAH in patients with MCTD from January 1972 to December 2020.*

Results. *The results were pooled using random-effects meta-analysis based on DerSimonian and Laird method. A total of 983 patients from eight studies were included in the meta-analysis (K=8, n=983). Pooled prevalence of PAH in MCTD patients was 12.53% [95% CI 8.30–18.48%] with significant level statistical heterogeneity (tau2=0.30, tau=0.55, i2 83.3%, H=2.13 Q(df,7) =31.90, p=0.001). There was no association between PAH and female gender or age. The percentage of deaths in MCTD patients due to PAH varied and reached up to 81.8%.*

Conclusion. *This is the first systematic review and meta-analysis investigating the prevalence of PAH in patients with MCTD and it revealed an overall prevalence of PAH in patients with MCTD of 12.53%. Our results showed trends of reduced prevalence of MCTD-PAH over last four decade, reconfirmed the lower prevalence rate in recent studies, but revealed an increased mortality rate. We also determined the low impact of the age, gender, and interstitial lung disease on MCTD-PAH.*

Introduction

Pulmonary hypertension (PH) is a severe condition that may occur in connective tissue diseases (CTDs) and is associated with morbidity and high risk of mortality. The World Health Organisation (WHO) has defined PH into five groups (group1-5) based upon aetiology and mechanisms (1-4). The updated clinical classification of PH according to the 2022 guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) consider Group 1 is the pulmonary arterial hypertension (PAH) of several conditions that include CTD; Group 2 (PH associated with left heart disease); Group 3 (PH associated with lung disease and/or hypoxia); Group 4 (PH associated with pulmonary artery obstructions); Group 5 (PH with unclear and/or multifactorial mechanisms) (5). Basically, pulmonary hypertension is defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest.

Mixed connective tissue disease (MCTD) is a rare disease that was first described in 1972 as a benign disease characterised by high titre of anti-U1RNP autoantibodies (Abs) and combined features of three related autoimmune rheumatic diseases- systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and polymyositis (PM) (6). Pulmonary involvement was not described at that time (6), but in 1980 as a less frequent vascular complication (7), however, the relation to PAH was unclear. Two later studies reported that the prognosis of patients with MCTD may vary from a benign to a severe progressive course (8, 9). Subsequent longitudinal studies revealed reduced anti-U1-RNP Abs and disease activity over several years indicating long-

term remission in patients with MCTD; however, a severe, progressive course of the disease could occur in one-third of the patients (10, 11). In recent years more complications have been reported in patients with MCTD (12). The most severe complication being MCTD-associated PAH (MCTD-PAH) that contributes to premature death (11).

Well-studied CTD-associated PAH (CTD-PAH) are SSc-PAH and SLE-PAH. The prevalence of SSc-PAH was estimated to be between 7.5–12% (13-15), while of SLE-PAH varied between 0.5–17.5% (16). However, the overall prevalence of MCTD-PAH needs to be clarified. In general, CTD-PAH had a poor prognosis. A multicentre-study demonstrated that in the modern therapy era, the prognosis improved in both SSc-PAH and SLE-PAH patients (17, 18), with a better prognosis in SLE-PAH compared to SSc-PAH (19, 20). The outcome of PAH in patients with other CTDs including MCTD is less clear. One earlier study showed a faster occurrence of PAH and shorter survival time in MCTD compared to SLE or SSc patients (17). Typically, the occurrence of isolated PAH has a better prognosis than PAH related to interstitial lung diseases (ILD). Patients with PAH were further classified as either PAH or ILD-associated PAH (ILD-PAH), thus, other underlying causes of PAH should be excluded (3). Isolated PAH was defined by the absence of ILD on high-resolution CT scan (HRCT) and/or forced vital capacity (FVC) >70% of predicted value, while ILD-PAH defined by lung involvement >5% on HRCT and a restrictive pattern (FVC<70%) on pulmonary function tests (PFTs) (21).

In this report we aimed to perform a systematic literature review on PAH in adult patients with MCTD since the disease discovery in 1972 up to 2020. We aimed to estimate the prevalence, mortality, and the predictors of MCTD-PAH, as well as the prevalence trend over the years.

Materials and methods

Data search

Two reviewers performed the search independently. The PubMed/Medline, Embase, Scopus and Web of Science electronic databases were searched for January 1972 to December 2020 period. No articles were retrieved from our search in Scopus and Web of Science databases. Only randomised controlled clinical trials (RCT) and observational/original studies in English language were reviewed. We also manually checked the references of included articles for potential inclusion. This review started as a scoping review to determine if there is sufficient and meaningful literature to synthesise. Thus, the systematic review and meta-analysis was not registered on PROSPERO. Using the two basic Boolean operators "AND, OR" we did comprehensive search using various combinations of the following keywords: "Mixed connective tissue disease" OR "MCTD" OR "rheumatic disease" OR "undifferentiated CTD" OR "overlap syndrome" OR "overlap disease" AND "Pulmonary arterial hypertension" OR "PAH" OR "RHC" AND "outcome" OR "deaths" OR "mortality". The full search strategy used according to MesH is available in Supplementary Table S1.

Study eligibility criteria

The RCTs and original articles in English, prospective or retrospective, in human adults aged ≥18 years which directly studied PAH in MCTD patients were included in this systematic review and meta-analysis. Studies on MCTD as part of all CTDs or rheumatic diseases were excluded. Information on ILD was included in most of the studies, so it has been analysed as evidence for pulmonary involvement in our study. Participants of unisex or lack of a control or placebo group were not the exclusion criteria. Reviews, systematic reviews and meta-analysis, letter to editor, and case reports were excluded. Studies that involved pregnant or breastfeeding women, children, adolescents, or mixed age groups (*i.e.* adults with adolescents or children) were also excluded. Exclusion criteria were similarly applied to any article if the publication year, author, or abstract was not available in the early search process.

Two reviewers participated in the initial selection of the studies according to our search strategy, the other three reviewers rechecked all selected studies according to our selection criteria. The four reviewers reviewed all study characteristics (Tables I and II) and data selection as in the PRISMA flow diagram (Fig. 1). All studies included in this review, with few exceptions, showed a clear methodology and subsequent report of their results.

Patients

Inclusion of patients in the MCTD cohort was based on the five following criteria: age18 years and above, clinical diagnosis of MCTD verified by a rheumatologist with a positive serum anti-U1 RNP antibody test in high titre, and fulfilment of at least one of the three known diagnostic criteria sets for MCTD: the modified Sharp criteria, the criteria of Alarcon-Segovia and Villa-real, and those of Kasukawa (6, 8, 9). As previously reported there was no statistical difference between the three diagnostic criteria sets used in our studies, indicating that they are comparable (8). None of the studies applied the fourth diagnostic criteria published by Kahn MF (22). PAH definition used in the current study is the definition for those presented as Group1 in the WHO functional classes (3). The PAH was diagnosed in all articles according to the guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) (23), the diagnosis of PAH confirmed by right heart catheterisation (RHC) to demonstrate a mean pulmonary arterial pressure (mPAP) ≥20 mmHg at rest (24). RHC in most of the studies was done at time of diagnosis, while in some patients the PAH was suspected by clinical criteria, then Doppler echocardiography (ECHO) was done first, and when the RVSP was ≥25 mm Hg at rest then RHC was performed to confirm the diagnosis. HRCT was known to be used either for the diagnosis or during follow up of PAH (25, 26).

Statistics

We performed a meta-analysis of proportions based on event rate (number of patients with PAH) and sample size (study sample size). The results are reported as pooled estimate proportion

Table I. Demographic data, clinical features, and autoantibodies in patients with mixed connective tissue disease in the eight studies included in the meta-analysis study.

No	1	2	3	4	5	6	7	8
Author	Sullivan WD *et al*. 1984 (31)	Burdt MA *et al*. 1999 (29)	Wigley FM *et al*. 2005 (44)	Vegh J *et al*. 2006 (30)	Hajas, A *et al*. 2013 (27)	Gunnarsson R *et al*. 2013 (28)	Kaneko T *et al*. 2014 (45)	Kawano-Dourado L *et al*. 2015 (32)
Country	Columbia	Columbia	USA+Canada	Hungary	Hungary	Norway	Japan	Brazil
Type of study MC / SC	Prospective cross-sectional. - SC	Prospective Cross-sectional study - SC	prospective & retrospective study - MC (50)	Prospective Cross-sectional study - SC	Prospective cross-sectional/ cohort study - SC	Prospective cross-sectional - MC	Prospective cross-sectional - SC	Retrospective cohort study - SC
Demographic data MCTD (ref) Dx criteria Pts no.	 MCTD [6,8,9] 34	 MCTD [9] 47	 MCTD [8] 194	 MCTD [6,8,9] 179	 MCTD [8] 280	 MCTD [6,8,9] 147	 MCTD [6,8,9] 63	 MCTD [9] 39
PAH pts % (no.)	29% (10)	23% (11)	9.3% (18)	13% (25)	17.8% (50)	3.4% (5)	7.94% (5)	5.13% (2)
Mean age ±SD/years (Range years)	29.1 ±NA (12-67)	31 ± 14 (NA)	62.4±13 (Ret G): 55.5 ±13.1 (Pro G):	36.8 ± 8.5 (25–65)	53.1 ± 12.6 (19–78)	45.6± NA (NA)	56.3± 16 ILD+ve: ILD-ve: 46.9±15	53 ± 11.3 (NA)
F:M (female: male)	31:3	43:4	NA	140:14	259:21	113: 34	57:6	All F = 39
Mean disease duration Mean follow-up (MFU)/year (range)	4.4 6.26 years NA	NA 15 ± 8 (3-29)	8.5±6.5 (RetrosG) (Pros G) 7.8±6.7 (≥1 year)	8.4 ±4.1 7 years MFU: NA	13.1 ± 7.5 NA (1-33)	10.2 5.6	13.8±2.35 ILD +ve: 14.5±1.40 ILD-ve: MFU: NA	19 (15-28) 10 years (7-9)
Clinical feature Polyarthritis no. (%)	 29 (85%)	 96%	 NA	 NA	 251 (89.6%)	 NA	 NA	 28%
Raynaud's phenomenon No (%)	31 (91%)	96%	NA	24 (96%) PAH 144 (93%) non-PAH	161 (57.5%)	NA	NA	38%
Myositis no. (%)	27 (79%)	51%	NA	21 (84%) PAH 152 (98%) non-PAH	91 (32.5%)	NA	NA	NA
Serositis no. (%)	NA	34%	NA	8 (32%) PAH 23 (15%) non-PAH	NA	NA	NA	NA
Esophageal dysmotility no. (%)	One patient	66%	NA	15 (60%) PAH	139 (49.6%)	NA	NA	90%
ILD-PAH no (%)	NA	NA	NA	16% (4)	18%	NA	NA	18%
Others (clinical features of PM/SLE/PSS)	Malar rash Renal Anaemia Lymph adenomegaly	NA	NA	Photosensitivity	NA	NA	NA	Sclerodactyly weak muscle High CK 41% Photosensitivity
Therapy Immunosuppressant therapy	 CS, CyC, HCQ, AZA	 CS, cytotoxic therapy	 NA	 CS CyC	 CS CyC MTX	 NA	 CS	 CS, CyC AZA, MTX, HCQ
PAH treatment	NA	NA	Bosentan epoprostenol	Vasodilators anticoagulants	Proteinoids, PDE-5 Inh.	NA	NA	NA
Autoantibodies Anti-U1RNP:(pts %)	 100%	 100%	 100%	 100%	 100%	 100%	 100%	 100%
Anti-CL IgG/IgM: no. (%)	IgG; 15.71 (18.49%)	25%	NA	IgM;16 (46%) IgG; 3 (12%)	98 (35%)	NA	NA	2%
AECA: no. (%)	8.06 (9.3)	NA	NA	16 (64)	94 (33.57)	NA	NA	NA
Anti-Sm: no. (%)	NA	22%	NA	NA	19 (6.79)	NA	NA	NA
Ds-DNA: no. (%)	NA	19%	NA	NA	9 (3.21)	NA	20 (31.75)	0%
Ro/SSA: no. (%)	NA	29%	NA	NA	92 (32.86)	NA	NA	26%
La/SSB: no. (%)	NA	4%	NA	NA	NA	NA	NA	2.5%
RF: no. (%)	NA	NA	NA	NA	NA	NA	NA	26%
Anti-CCP: no. (%)	NA	NA	NA	NA	53 (18.93)	NA	NA	NA

MA: mean age; Dx criteria: diagnostic criteria; Pts: patients; NA: not available; AECA: anti-endothelial cell antibodies; Anti-CL: anti-cardiolipin antibodies; ILD: interstitial lung disease; -ve: negative; +ve: positive; APLs: antiphospholipid syndrome; Retros G: retrospective group; Pros G: prospective group; CS: corticosteroid; CyA: cyclosporine A; HCQ: hydroxychloroquine; CyC: cyclophosphamide; AZA: azathioprine; MTX: methotrexate; PAH: pulmonary arterial hypertension; MCTD: mixed connective tissue diseases; PDE-5 Inh: phosphodiesterase-5 inhibitor.

Table II. Pulmonary arterial hypertension in patients with mixed connective tissue diseases prevalence and definitions in the eight studies included in the meta-analysis study.

No	1	2	3	4	5	6	7	8
Author	Sullivan WD *et al*. 1984 (31)	Burdt MA *et al*. 1999 (29)	Wigley FM *et al*. 2005 (44)	Vegh J *et al*. 2006 (30)	Hajas A *et al*. 2013 (27)	Gunnarsson R *et al*. 2013 (28)	Kaneko T *et al*. 2014 (45)	Kawano-Dourado L *et al*. 2015 (32)
Country	Columbia	Columbia	United States (USA)	Hungary	Hungary	Norway	Japan	Brazil
Type of study MC / SC	Prospective cross-sectional. - SC	Prospective Cross-sectional study - SC	prospective & retrospective study - MC (50)	Prospective Cross-sectional study - SC	Prospective cross-sectional/ cohort study - SC	Prospective cross-sectional - MC	Prospective cross-sectional - SC	Retrospective cohort study - SC
Total patients no.	34	47	194	179	280	147	63	39
PAH pts % (no.)	29.4% (10)	23.4% (11)	9.3 % (18)	13.9% (25)	17.85% (50)	3.4% (5)	7.94% (5)	5.13% (2)
Method of screening	-FANA -PFT - ECHO	HLA–DR typing. Serology, clinical	Questionnaire -PFT -Serology	Clinical Dopplar ECHO	PFT & DLCO Doppler ECHO HRCT	PFT, HRCT, ECHO NT-proBNP	NA	PFT HRCT ECHO
Method of diagnosis of PAH (Dx)	- RHC - ECHO - PFT	- RHC - Serology - clinical	-RHC -ECHO -PFT	RHC (mPAP≥ 98 mmHg)	RHC (mPAP≥ 25) HRCT Lung biopsy	RHC (mPAP≥ 25mmHg)	NA	RHC (mPAP>40 mmHg) -ECHO
Method of follow up	NA	Clinical features	NA	NA	ECHO then RHC if required	ECHO RHC	NA	HRCT/ILD scores
Classifications no. of pts (%) - PAH - ILD-PAH - ILD	10 PAH (29.4%) - No ILD	11 PAH (23.4%) - No ILD	18 PAH (9.3%) - No ILD	25 PAH (13.9%) 4 ILD-PAH (2.2%) 92 ILD (51.4%)	50 PAH (17.8%) NA 132 ILD (47.1%)	-2 PAH (1.3%) -3 ILD-PAH (2%) -40 ILD (80%)	-3 PAH (4.7%) -2 ILD-PAH (3.1%) -21 ILD (33.3)	-2 PAH (5.13%) - -30 ILD (77%)
PAH no. (%) at: - inclusion - during study -Total (T) at end of study	-NA -10 (29%) T=10	- zero 11(23%) T=11	- 11 (5.7%) - 7 (3.6%) T= 18	-25 (13.9%) - zero T=25	zero 50 (17.8%) T= 50	3 (2.0%) 2 (1.3%) T=5	- 5 (7.94%) -zero T=5	1 (2.5%) 1 (2.5%) T=2
PFT: means of DLCO (mmol/kPa/min), (% predicted)	NA	NA	-Pts with RVSP > 40 mmHg: DLCO: 58.9 (24)	NA	NA	3.2 (40), 2.1 (28), 1.2 (16), 2.9 (34), 4.2 (60)	NA	PFT 33pts (17 (51.5% had abnormal PFT)
FVC % predicted.	VC: 34%	NA	FVC: 82.9%	NA	NA	-2 (39), 1.8 (67)	NA	*17.7 ± 5.1 71%
FEV1 % predicted.	10%	NA	-Pts with RVSP <40mmHg 71.9(19.7) FVC:88% FEV1: NA	NA	NA	1.2 (50), 0.9 (29), 2.3 (92) -1.1 (43), 1.5 (69), 1.1 (51), 0.9 (34), 1.4 (67)	NA	*2.58 ± 0.54 78% *2.13 ± 0.44 81%
HRCT pts % (test's finding)	NA	NA	NA	NA	16 ILD 3 PAH	2 Normal 3 Fibrosis	NA	37 (94%) abnormal ILD scores (77%)
mPAP (mmHg) by RHC mentioned for	for 15 high in 10 /15 mPAP >25 mmHg	NA	for 7 >25mmHg	mPAP ≥ 98mmH	for 22 pts (mPAP≥ 25)	for the 5 pts (mPAP 45mmHg)	NA	for 5 pts (mPAP>40 mmHg)
MCTD-PAH deaths / out of total deaths in MCTD patients	4/34 deaths due to PAH	9/11 deaths due to PAH	NA	5 /12 deaths due to PAH	9/22 deaths due to PAH 3 TTP/UUS 3 infection &7 CVD	3/12 deaths due to PAH	NA.	-3 deaths ILD - no PAH deaths
PAH-Death %	12%	81.8%	NA	41.7%	40.9%	25%	NA	0%
Survival rate (SR) from Dx in months or years	NA	19 patients had clinical remission	NA	20 yrs SR PAH pt 70% Non-PAH pts: 90%	5 yrs SR 98%, 10 yrs SR 96%, 15 yrs SR 88%	8,14,33, 45 & 182 months (mean= 56.5 months)	NA	NA
Comorbidities no. of pts (%)	CVD :9 (26.4%) Lymphadenopathy: 19 (50) Pulmonary: 29 (85.2)	CVD-Pericarditis 6 (12.1) Renal: 2(4.2)	NA	NA	-CVD 98 (35), 72 (25.7) APL, 11 (3.9) renal, 102 (36.4) skin, 56 (20) CNS, 16(5.7) cancer, 3 TTP	NA	12 (19.04) SjS	CVD 4 (10) pericarditis 5 (13) SjS

ECHO: echocardiography; HRCT: high-resolution computed tomography; PFT: pulmonary function tests; PF: pulmonary fibrosis; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; RVSP: right ventricular systolic pressure; RHC: right-sided heart catheterisation; SjS; Sjögren's syndrome; DLCO: diffusion lung capacity; mPAP: mean pulmonary atrial pressure; MC: multicentre; SC: single centre; PAH: pulmonary arterial hypertension; MCTD: mixed connective tissue diseases; Dx: diagnosis

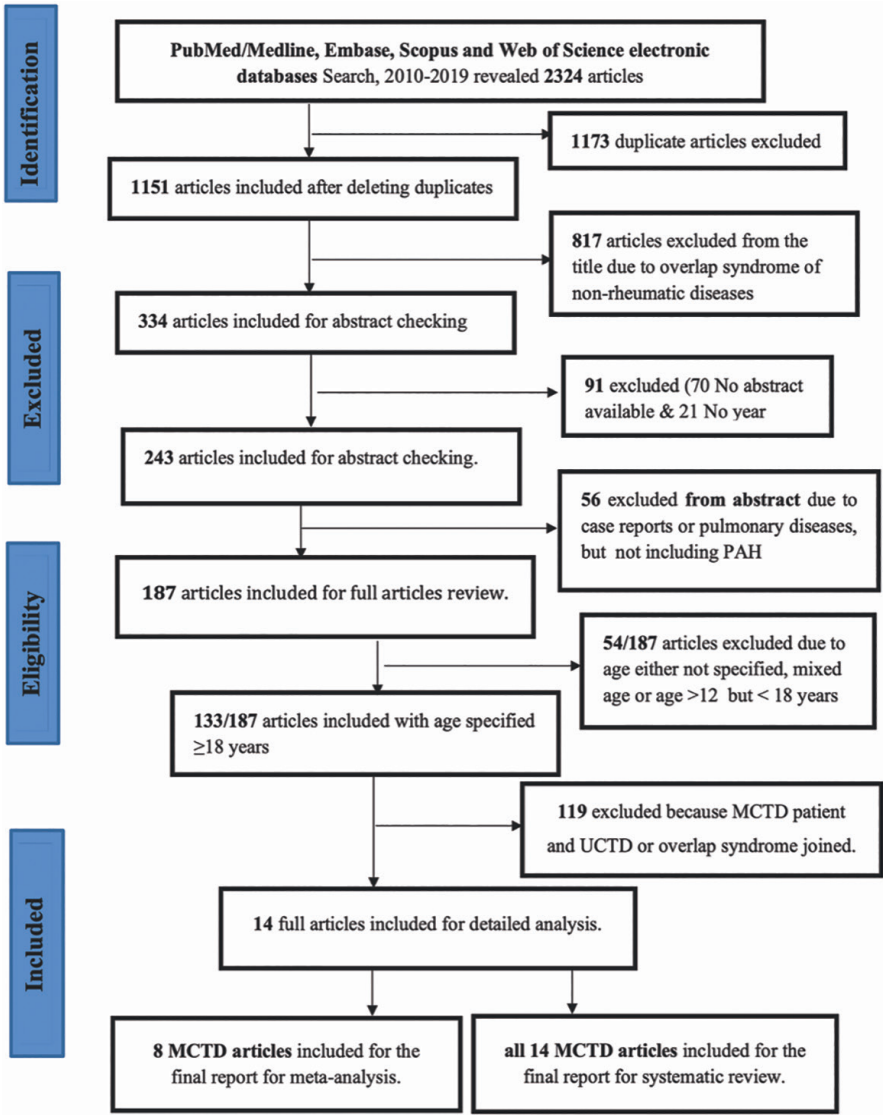

Fig. 1. PRISMA flow diagram for pulmonary arterial hypertension in patients with mixed connective tissue disease.
CTD: connective tissue disease. MCTD: mixed CTD. UCTD: undifferentiated CTD. PAH: pulmonary arterial hypertension.

and 95% CI. We used random-effects modelling analysis with an assumption that there is not only one true effect size, instead, a distribution of true effect sizes. Moderator analysis was performed on the variables age and sex using meta-regression. All statistical analyses were performed using R v. 3.5.3 with the meta for the package.

Results of meta-analysis study

A PRISMA flow diagram for this study depicted in Figure 1 shows the procedure to identify the eight articles included for the meta-analysis (Table I). Demographic data, clinical features, autoantibodies, and medications on patients with MCTD in these studies are presented in Table I. The results were pooled using random-effects meta-analysis based on the DerSimonian and Laird method (Fig. 2). A total of 983 patients with MCTD from the eight studies were included in the meta-analysis that investigated the prevalence of PAH in patients with MCTD, of whom 71.82% (706) were females (Fig. 4-5).

The Forest plot of the meta-analysis depicting the prevalence of PAH among patients with MCTD is presented in Figure 2. Among the total of 983 patients with MCTD, 126 patients were found to have PAH. Pooled results suggest a prevalence of 12.53% [8.30%; 18.48%] using random effects model among patients with MCTD (Fig. 2). Quantifying heterogeneity: tau2 = 0.3063 [0.1225; 2.3240]; tau = 0.5535 [0.3500; 1.5245], I2 = 78.1% [56.7%; 88.9%]; H = 2.13 [1.52; 3.00]. Funnel plot of meta-analysis of the prevalence of PAH among patients with MCTD is depicted in Figure 3. Test of heterogeneity: Q (d.f.,7) =31.90, P=0.0001. Visual inspection to the funnel plot Figure 3 reveals that there was no publication bias. Meta-regression of age on the prevalence of PAH among patients with MCTD is shown in Figure 4. This figure revealed that age was a significant moderator QE (d.f., 6) = 16.70, p=0.004. Meta-regression of gender on the prevalence of PAH among patients with MCTD is presented in Figure 5, which showed that gender (% female) was not a significant moderator QM (d.f.,1) = 0.09, p=0.75.

Next, we analysed the prevalence of PAH over time in the eight studies included for the meta-analysis summarised in Table II. We observed a lower prevalence of PAH in patients with MCTD over time: 29% (1984), 23% (1999), 9.3% (2005), 13% (2006), 17.8% (2013), 3.4% (2013), 7.9% (2013), 5.1% (2015). Table II also displays the number of MCTD patients according to the classifications of PAH with or without ILD. In our meta-analysis isolated PAH was found in 93% of the patients, while only 6% of the MCTD patients had both PAH and ILD (ILD-PAH) in three studies with available information. We also analysed the percentage of deaths in six articles with available information (Table II): In one study total number of deaths was 22 (22/208), 9 of the 22 deaths were among the MCTD-PAH cohort (9/22, 40.91%) (27). In another study, the total number of deaths was 12 (12/147, 8.2%), although the number of MCTD-PAH was low (5 patients only) 3 of the deaths were among the MCTD-PAH patients (3/12, 25%) (28). In other studies the number of deaths was 9/11, 81.8% (29) , then 5/12, 41.7% (30) , 4/34, 12% (31) and in the earliest study the total number of deaths was 3 only 3/39 patients (7.69%), none of them within the PAH subgroup (32).

Results of the systematic literature review

In the current systematic review, we identified 14 studies investigating the prevalence of PAH in patients with MCTD. The data presented in Table III show 14 studies from different countries: Hungary (n=5), Norway (n=3), three from Columbia (n=3), one each from United States and Canada joint study (n=1), Brazil and Japan. Table III, depicts the demographic data, total number of patients, clinical features, autoantibodies, and medications reported by these studies. The prevalence of PAH in the 14 studies included for the systematic literature review from old to recent (1972–2020) is also presented in Table III. Additionally, Table III demonstrates the screening, diagnosis (RHC) and follow up methods of MCTD-PAH cohort, but also MCTD-PAH patients with or without ILD, and also illustrates the number of deaths.

Discussion

To our knowledge, this is the first systematic literature review and meta-analysis on PAH in patients with MCTD since the disease itself or the pulmonary manifestations of the disease were first described in 1972 and 1980, respectively (6, 7). Currently, there is limited data on the prevalence, diagnosis and mortality of PAH in patients with MCTD. In conducting this review, we aimed to identify the overall prevalence of PAH in patients with MCTD. We also aimed to investigate if there were any prognostic factors such as age or gender associated with PAH in patients with MCTD. Our study revealed an overall prevalence of PAH in patients with MCTD of 12.53% which is lower than previously reported. We also found a lower impact of the ILD, age, and gender on MCTD-PAH, but higher mortality rate than previously reported.

In our systematic literature review we identified a total of 14 studies investigating PAH in patients with MCTD (Table III). However, 6/14 studies were from the same countries or from the same centres with publication years very close. To avoid overlapping of cohorts, only one study from those countries was included for the meta-

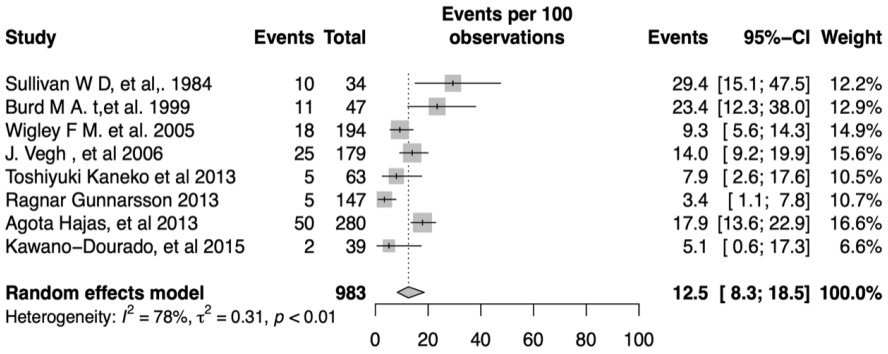

Fig. 2. Forest plot of the meta-analysis of the prevalence of pulmonary arterial hypertension in patients with mixed connective tissue disease.

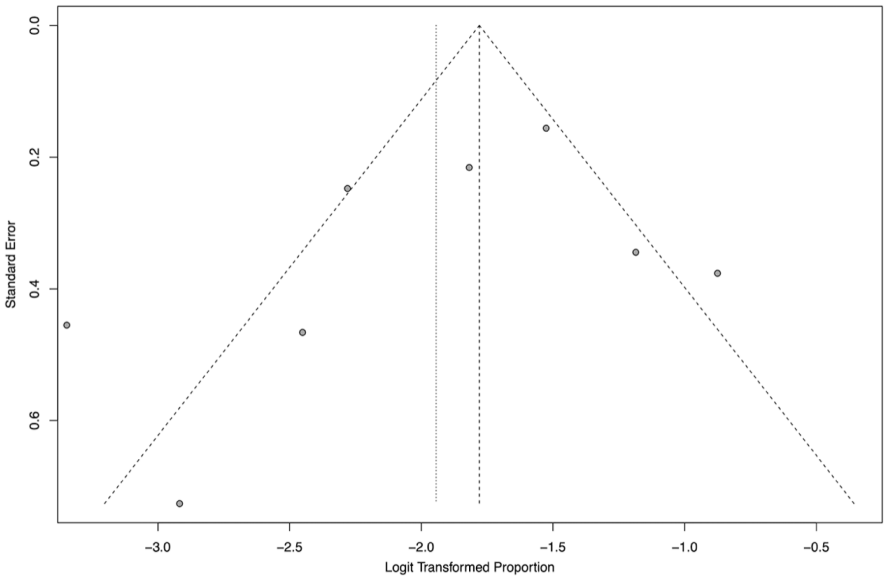

Fig. 3. Funnel plot of the publication bias of the prevalence of prevalence of pulmonary arterial hypertension in patients with mixed connective tissue disease.

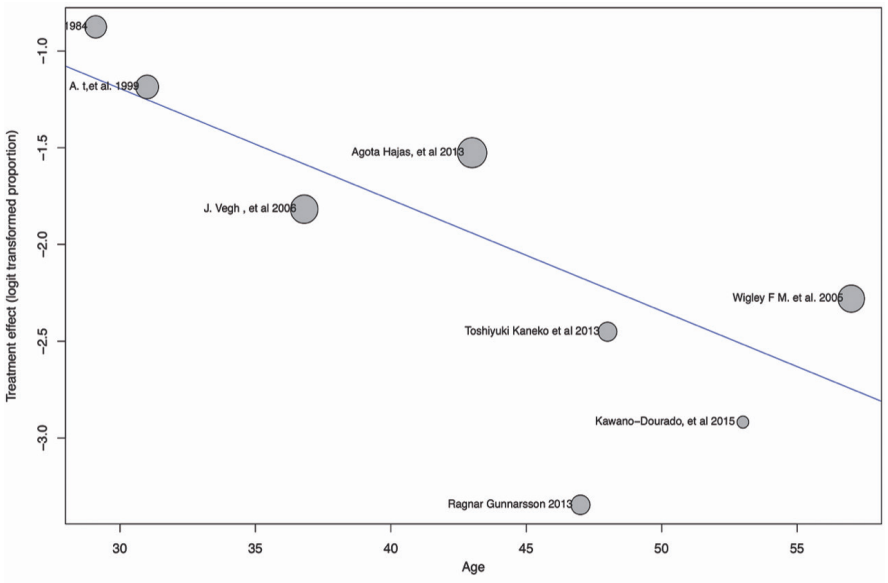

Fig. 4. Meta-regression of age on the prevalence of prevalence of pulmonary arterial hypertension in patients with mixed connective tissue disease.

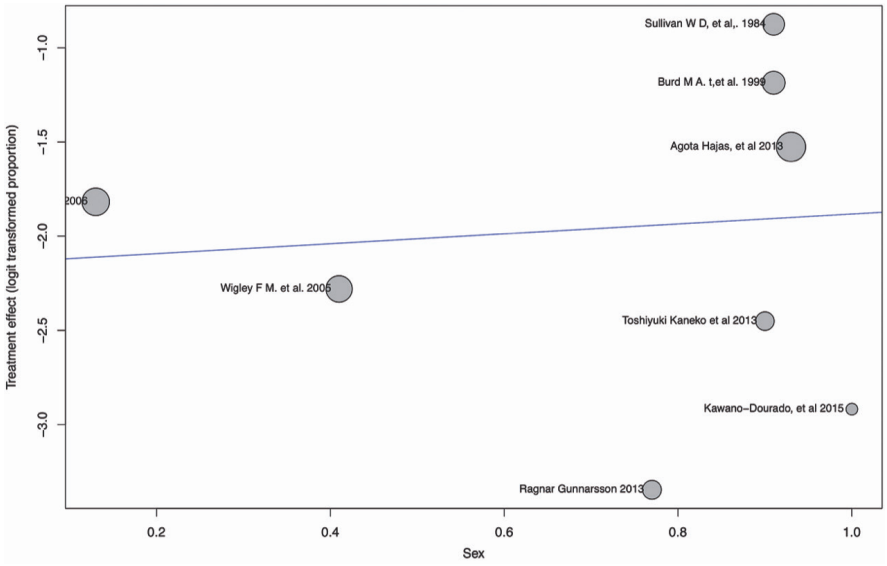

Fig. 5. Meta-regression of sex (%female) on the prevalence of prevalence of pulmonary arterial hypertension in patients with mixed connective tissue disease.

analysis (8/14). Two studies one each from Hungary and Columbia, were included in the meta-analysis because both these were prospective, 7 and 15 years apart, and unlikely to represent the same cohort. Accordingly, eight of the 14 studies were included in the meta-analysis (Tables I and II). The number of patients included, 983, is considered large for such rare disease as MCTD, and with a range of follow up periods of 1–33 years in all studies. The over-all prevalence of PAH in the current meta-analysis study is 12.53% (12.5%), ranging from 3.4–29%, which is higher than that of SSc-PAH and SLE-PAH (13-16). Interestingly, our results revealed a declining trend in the prevalence of PAH over the years and the highest prevalence 29% was in the first study in 1984 and dropped below 10% in the most recent three studies. The decline in the prevalence of PAH over the years could be explained by advances in diagnosis methods, clarity on definition and diagnostic criteria for PAH, and availability of new therapies to prevent clinical complications.

A strength of our study is that the diagnosis of PAH was based on right heart catheterisation (RHC), the gold standard method for the diagnosis, which was confirmed in seven of the eight studies while in one study the method of the PAH diagnosis was not stated. In three studies, echocardiography (ECHO) was used first to calculate the mean systolic pulmonary artery pressure (mPAP), and due to a significant risk of over-estimation, then the diagnosis was confirmed by RHC, although the ECHO method has been used by some studies as in Sjögren's syndrome and rheumatoid arthritis, to estimate the prevalence of PAH (33-35). The eight studies included in the meta-analysis were heterogenous and differed in their design and were not easy to compare. Only four studies provided detailed data on PFT, HRCT, or ECHO, which were the main methods to screen for PAH, and according to results, they would decide which patient should be further evaluated by the RHC procedure. On the other hand, detailed data regarding the RHC itself such as the total number of patients who underwent the procedure or the exact levels of mPAP were available in some of the studies. In our present study, isolated PAH was found in 93% of the patients, while only 6% of the MCTD patients had ILD-PAH. Although data for this group was available only in three studies, yet it suggests that the PAH in patients with MCTD is rarely due to pre-existing ILD. Our results in this perspective are consistent with another study, which demonstrated that PAH in MCTD contributes to premature death and associates with proliferative vascular abnormalities involving small pulmonary vessels, rather than ILD (11). PAH in MCTD patients could be different from PAH in systemic sclerosis (SSc), where most of the patients had severe pre-capillary PAH in the presence of significant coexisting ILD (15). Furthermore, we investigated the association between the prevalence of PAH among MCTD patients with age and gender as predictive factors. Our meta-regression analysis results showed that neither the age nor the gender of the MCTD patients predicted the percentage of PAH among MCTD patients.

Due to the limited number of studies, and the inconsistency in reporting if the cause of death was due to PAH or not, we were unable to assess the relation to PAH in few studies. In the six cohorts included in our metanalysis results the percentage of deaths in the MCTD-PAH cohorts varied from 0 to 81.8%. The reason for wide variations is not clear but might be due to patient selection in different studies. Although, there was a large variation in mortality rate in patients with MCTD-PAH, still PAH may have a substantial negative effect on survival rate in patients with MCTD. A recent French national multicenter study in 2023 concluded that PAH is a rare but severe and a leading cause of death in MCTD patients with the 10-year survival rate 56% (36). Generally, the mortality in patients with PAH is associated with the extent of right-sided heart failure (37, 38). In our study the number of deaths among MCTD-PAH cohorts was well documented but the details of deaths were not.

To date, the characteristic features of MCTD, in addition to all clinical features listed in the four known diagnostic criteria that also share the presence of high anti-U1snRNP antibody titre in serum, a high frequency of HLA-DR4, presence of increased serum levels of the cytokine TNF early in the disease, and an association with a unique haplotype (10, 39-43). Our current meta-analysis study added the overall prevalence of PAH to be 12.53%, with a declining trend over the years, and high mortality rate due to PAH in patients with MCTD.

Limitations and strengths of the study

One of the strengths of the current meta-analysis study was that the MCTD

Table III. The characteristics and the prevalence of pulmonary arterial hypertension in patients with mixed connective tissue diseases in the 14 studies included in the systematic literature review study for the period 1972-2020.

no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Author	Alpert MA *et al.* 1983 (46)	Sullivan, WD *et al.* 1984 (31)	Burdt MA *et al.* 1999 (29)	Wigley FM *et al.* 2005 (44)	Vegh J *et al.* 2006 (30)	Soltesz1 P *et al.* 2010 (48)	Hajas A *et al.* 2011 (49)	Szodoray P *et al.* 2012 (47)	Gunnarsson R *et al.* 2012 (50)	Gunnarsson R *et al.* 2013 (28)	Hajas A *et al.* 2013 (27)	Kaneko T *et al.* 2014 (45)	Kawano-Dourado L *et al.* 2015 (32)	Reiseter S *et al.* 2017 (51)
Country	Columbia	Columbia	Columbia	United states and Canada	Hungary	Hungary	Hungary	Hungary	Norway	Norway	Hungary	Japan	Brazil	Norway
Type of study MC / SC	Prospective cross-sectional SC	Prospective cross-sectional SC	Prospective Cross-sectional study (SC)	prospective and retrospective survey MC (50)	Prospective Cross-sectional study SC	Prospective cross-sectional Study SC	Prospective cross-sectional study SC	Prospective longitudinal study SC	Retrospective Cross-sectional/ cohort study SC	Prospective cross-sectional MC	Prospective cross-sectional/ cohort study SC	Prospective cross-sectional SC	Retrospective cohort study SC	Observational cohort SC
MCTD (ref) Dx criteria	MCTD (6,8,9)	MCTD (6,8,9)	MCTD [9]	MCTD [8]	MCTD (6,8,9)	MCTD [8]	MCTD (6,8,9)	MCTD (6,8,9)	MCTD (6,8,9)	MCTD (6,8,9)	MCTD [8]	MCTD (6,8,9)	MCTD [9]	MCTD (6,8,9)
Patients (Pts) no.	38	34	47	194	179	50	125	201	126	147	280	63	39	118
PAH pts % (no.)	29% (11)	29.4% (10)	23.4% (11)	9.3% (18)	13.9% (25)	24% (12)	32.8% (41)	23.88% (48)	3.96% (5)	3.4% (5)	17.85% (50)	7.94% (5)	5.13% (2)	4.2% (5)
Method of screening	-Clinical -serological -ECHO -PFT	-FANA -PFT	HLA–DR typing -Serology -clinical	-Dyspnea questionnaire -PFT -Serology.	Clinical	PFT, HRCT	PFT, HRCT	PFT, HRCT	PFT, HRCT, RHC	PFT, HRCT, ECHO NT-pro-BNP	PFT & DLCO. Doppler ECHO HRCT	NA	PFT HRCT	PFT & DLCO RHC
Method of diagnosis of PAH (Dx)	-RHC -ECHO -pulmonary haemody-namic	-RHC ECHO -PFT	-RHC -Serology -clinical	-RHC -Doppler echocardio-graphy -PFT	-RHC -Serology	ECHO (Carotid duplex ultrasound) (IMT)	Carotid duplex ultrasound (ECHO) (IMT) & RHC	- ECHO - Lung biopsy (7 cases) - Transbron-chial Biopsy (8 cases)	RHC (SBP>40 mmHg) precapillary PAH by RHC	RHC According to the 2009 European guidlines1	RHC (if SBP≥ 25) HRCT Lung biopsy (open & Transbron-chial)	NA	ECHO with RHC (SBP>40 mmHg)	HRCT RHC
Method of follow up	RHC	NA	Clinical features	NA	NA	NA	NA	ECHO	RHC	ECHO RHC	ECHO then RHC if required	NA	HRCT scores % (ILD score)	HRCT
Follow up (FU) in years (yrs) (mean)	NA	Mean FU: 6.26 years	15 +- 8 years		7 yrs (1995--2002)	NA	NA (12.96±7.47)	25 yrs (NA)	4.2 yrs (NA)	NA (NA)	1-32 yrs (13.1 ± 7.5)	NA NA	10 yrs (NA)	6.4 yrs (NA)
IMT mm Mean (SD)	NA	NA	NA	NA	NA	0.64 (± 0.13)	0.65 (±0.14)	NA	NA	NA	NA	NA	NA	NA
Classifications no. of pts (%)	11 (29%) PAH	10 (29%) -PAH	-11 (23%) PAH	- 18 PAH (9.3%)	25 PAH 96 ILD (4 with PAH)	-12 (24) PAH - -40 (80) ILD	-41 (32.8) PAH - -80 (64) ILD	-48 (23.8) PAH - -106 (52.7) ILD	-2 (1.59) PAH -3 (2.38) ILD-PAH -44 (34.9) ILD (PF)	-2 (%) PAH -3 (%) ILD-PAH -40 (80) ILD	-50 PAH (17.8%) - -132 ILD (47.1%)	-3 PAH (7%) -2ILD-PAH -21 ILD	-2 PAH (5%) - -30 ILD (77%)	-1 PAH -4 ILD-PAH -45 ILD
Pts no. of PAH at: - inclusion -during study -Total (T) at end of study	-zero -11 (29%) T=11(29%) Three died	-zero -10 (29.4%) - T= 10	-zero 11(23.4%) T=11 (23%)	-11 (5.7%) - 7 (3.6%) - T=18 (9.3%)	25 (13.9%) -zero -T= 25 (13.9%)	-12 (24%) - -T=12 (24%)	-41 (32.8) - -T=41 (32.8)	-48 (23.8) - -T= 48 (23.8)	- 3 (2.38) - 2 (1.59) -T= 5 (3.96)	-3 (2.0%) -2 (1.36) -T= 5 (3.4%)	- zero -50 (17.8) -T= 50 (17.8)	- 5 (7.94) - -T=5 (7.94)	-1 (2.5%) -1 (2.5) -T=2 (5.13%)	-5 (4.20) - T= 5 (4.20)
PFT: means of DLCO (mmol/kPa/min), (% predicted)	NA	NA	NA	Patient with ERVSP > 40 mm Hg: DLco: 58.9 24.1%	NA	NA	NA	NA	For 3 groups** *1.7 (91), 2.2 (89), 1.3 (78)	*3.2 (40), 2.1 (28), 1.2 (16), 2.9 (34), 4.2 (60)	NA	NA	PFT 33pts (17, (51.5% had abnormal PFT) *17.7 ± 5.1 71% *2.58 ± 0.54 (77%) reduced to 78% *2.13 ± 0.44 (83%) reduced to (81%)	DLCO % of predicted 0.94 (0.92, 0.97)
FVC% predicted	NA	VC: 34%	NA	FVC: 82.9%	NA	NA	NA	NA	*3.6 (94), 3.4(89),	*1.2 (39), 1.8 (67)	NA	NA		FVC % of predicted 0.95 (0.93, 0.98)
FEV1% predicted	NA	10%	NA	Patient with ERVSP <40 mmHg: 71.9 19.7% FVC: 88.2% FEV1:NA	NA	NA	NA	NA	2.8 (83) *2.9 (90), 2.7 (82), 2.3 (82)	1.2 (50), 0.9 (29), 2.3 (92) *1.1 (43), 1.5 (69), 1.1 (51), 0.9 (34), 1.4 (67)	NA	NA		

no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Author	Alpert MA *et al.* 1983 (46)	Sullivan, WD *et al.* 1984 (31)	Burdt MA *et al.* 1999 (29)	Wigley FM *et al.* 2005 (44)	Vegh J *et al.* 2006 (30)	Soltesz1 P *et al.* 2010 (48)	Hajas A *et al.* 2011 (49)	Szodoray P *et al.* 2012 (47)	Gunnarsson R *et al.* 2012 (50)	Gunnarsson R *et al.* 2013 (28)	Hajas A *et al.* 2013 (27)	Kaneko T *et al.* 2014 (45)	Kawano-Dourado L *et al.*	Reiseter S *et al.* 2017 (51)
HRCT pts % (test's finding)	NA	NA	NA	NA	NA	NA	NA	52% 35% fibrosis	65 (52%) abnormal reticular patterns: (Ground-glass 2 (2%). septal thickening 10 (8%) Nodules 7 (6%) Bronchiectasis 11 (9%)	2 Normal 3 Fibrosis	16 ILD 3 PAH	NA	-HRCT 37 (94%) 77% had abnormal scores - 11.3% (abnormal ILD score)	-49 pts ILD -70 ILD -ve 5 PAH pts
mPAP mmHg mentioned	NA	for 15 high in 10/15	NA	For 7	NA	NA	NA	for 20 pts	for the 5 pts	for 5 pts (45mmH)	for 22 pts	NA	NA	NA
Prognosis / Deaths	-3 deaths (3/8)	Death 12%	-11 deaths total -9 of the 11 deaths PAH	NA	Out of the 25 PAH 5 died	NA	NA	-16 deaths total -8 deaths PAH, 50% (During 25 yrs FUP)	10 deaths (7.9%) 8 (with abnormal HRCT) & 2 with normal HRCT (20.8% PF)	3 deaths 2 alive	22 deaths total 9 PAH (41 alive) 3 TTP/UUS 3 infection &7 CVD	NA	3 deaths ILD no PAH deaths	NA
Survival rate (SR) from Dx in years/months	NA	NA	19 had clinical remission	NA	20 yrs 70%PAH 90% Non-PAH	NA	NA	SR lower in pts with PAH	NA	8,14,33, 45 & 182 months (mean of 56.5)	5 yrs 98%, 10 yrs 96%, 15 yrs 88%	NA	NA	NA
Cardio-vascular disease	25 pts	9 (26.4%)	Pericarditis 6 (12.1%)	NA	NA	23 (46)	63 (50.4)	201 48 cardio-myopathy	16 (12.69) -pericarditis	NA	ischaemic, arrhythmia, valvular cardiomyo-pathy,	NA	4 (10%) pericarditis	NA
Mean mmHg ±SD SBP DBP	SBP: 87mmHg	SBP: 139mmHg DBP: 81 mmHg	NA	NA	SBP>130 DBP>90	137.4±21.1 90.9±15.9	139.76±22.3 86.56 (10.52)	40-50 mmHg 40-50 mmHg	SBP>40 mmHg NA	SBP > 45 mmHg NA	SBP >60 mm Hg NA	NA NA	NA NA	NA NA
vWFAg (%)	NA	NA	NA	NA	21 (84%)	224.1±115	210.38 (100.95)		NA	NA	NA	NA	NA	NA
Comorbidities no. of pts (%)	CVD 25 (65%)	CVD :9 (26.4 %) Lympha-denopathy: 19 (50%) Pulmonary disease: 29 (85.2 %)	Renal Disease: 2(4.2%) Pericarditis 6 (12.1%)	NA	NA	CVD: 23 (46%) 15 (30%) 2ndry APL	CVD: 63 (50.4%) 53 (42.4%) 2ndry APL	CVD (48) Osteoporosis 65 (32), DM, 4 (%), #spine 38 (18.9), thyroiditis 64 (31.8), 74 (36.8) SjS, 16 cancers	CVD 16 (12.69)	NA	CVD 98 (35), TTP 3 APL 72 (25.7), renal 11 (3.9), skin 102 (36.4), 56 (20) CNS, 16 (5.7) cancer	12 (19.04%) SjS	5 (13%) SjS	NA

ECHO: echocardiography; HRCT: high-resolution computed tomography; PFT: pulmonary function tests; PF: pulmonary fibrosis; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; 6MWDT: 6-min walking distance test (m); IMT: Carotid artery intima media thickness; RHC: right-sided heart catheterisation; SjS; Sjögren's syndrome; DLCO: diffusion lung capacity; mPAP: mean pulmonary atrial pressure; MC: multicentre; SC: single centre; PAH: pulmonary arterial hypertension; MCTD: mixed connective tissue diseases; Dx: diagnosis

patients in all studies were derived from unselected cohorts. Additionally, seven of the eight studies were prospective studies, among them six were prospective cross-sectional cohort studies and one was a prospective longitudinal study, the remaining study was a retrospective cross-sectional cohort study. One more potential strength of the current meta-analysis was that it includes one big multicentre study, where fifty centres (46 in the United States and 4 in Canada) participated in the study (44). The main limitation of the present study is the data insufficiency as many reports lacked data about survival rate, the exact cause of death or risk factors for the development of PAH. Again, duration of follow up or loss to follow- up and PAH-specific therapies of vasodilators have not been clearly presented in all studies. One more limitation is that the levels of mPAP and the wedge pressure were not mentioned in several of the studies. Furthermore, the studies are heterogenous in their design making it difficult to have one single conclusion apart from the prevalence and the mortality. However, for the first time we present data for PAH from a reasonably

large MCTD population from all-over the world during a period of five decades, with long duration of follow-up in most of the studies, also our main results are supported by both old and more recently published data.

Conclusions

The current study revealed that the overall prevalence of PAH in patients with MCTD was 12.53%, which is lower than previously reported. Our results described the trends of reduced prevalence of PAH over the years. We also reported low impact of ILD, age, and gender on MCTD-PAH. MCTD-PAH still has a significant effect on mortality. Therefore, there is a need for early detection, classification, and early treatment to reduce the mortality and to increase the survival rate. Additional efforts are crucial to demonstrate the definite class of PAH, to investigate its pathogenesis and to evaluate the currently available therapies for PAH in patients with MCTD.

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