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► To cite this version:

Benjamin Chaigne, Kevin Chevalier, Athenaïs Boucly, Christian Agard, Antoine Baudet, et al.. In-depth characterization of pulmonary arterial hypertension in mixed connective tissue disease: a French national multicenter study. *Rheumatology*, 2023, 62 (10), pp.3261-3267. 10.1093/rheumatology/kead055 . hal-03973280

HAL Id: hal-03973280

<https://hal.science/hal-03973280v1>

Submitted on 11 Jan 2024

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In-depth characterization of pulmonary arterial hypertension in mixed connective tissue disease: a French national multicentre study

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Keywords:

pulmonary arterial hypertension, MCTD, SLE, SSc, survival.

Abstract

Objective:

Pulmonary arterial hypertension (PAH) is a leading cause of death in MCTD. We aimed to describe PAH in well-characterized MCTD patients.

Methods:

MCTD patients enrolled in the French Pulmonary Hypertension Registry with a PAH diagnosis confirmed by right heart catheterization were included in the study and compared with matched controls: MCTD patients without PAH, SLE patients with PAH and SSc patients with PAH. Survival rates were estimated by the Kaplan–Meier method and risk factors for PAH in MCTD patients and risk factors for mortality in MCTD-PAH were sought using multivariate analyses.

Results:

Thirty-six patients with MCTD-PAH were included in the study. Comparison with MCTD patients without PAH and multivariate analysis revealed that pericarditis, polyarthritis, thrombocytopenia, interstitial lung disease (ILD) and anti-Sm antibodies were independent predictive factors of PAH/PH in MCTD. Estimated survival rates at 1, 5 and 10 years following PAH diagnosis were 83%, 67% and 56%, respectively. MCTD-PAH presentation and survival did not differ from SLE-PAH and SSc-PAH. Multivariate analysis revealed that tobacco exposure was an independent factor predictive of mortality in MCTD-PAH.

Conclusion:

PAH is a rare and severe complication of MCTD associated with a 56% 10-year survival. We identified ILD, pericarditis, thrombocytopenia and anti-Sm antibodies as risk factors for PAH in MCTD and tobacco exposure as a predictor of mortality in MCTD-PAH.

Introduction

MCTD, also known as Sharp's syndrome, is a rare CTD characterized by the presence of antibodies targeting the U1 small nuclear ribonucleoprotein particle (U1-snRNP) along with clinical features of other CTDs such as SSc, SLE or idiopathic inflammatory myopathy (IIM). These features commonly comprise RP, 'puffy' fingers, arthritis, myositis, pleuritis, pericarditis and symptoms of interstitial lung disease (ILD). Due to the rarity of the disease, there are no specific clinical practice guidelines regarding the management of MCTD patients [1] and experts agree on the need for further studies dedicated to MCTD.

In recent decades, several advances have been made in understanding the pathogenesis and disease course of MCTD. Although controversy about MCTD remains and disagreements regarding classification criteria persist, MCTD is a useful diagnosis, as it identifies patients who require long-term follow-up. Indeed, at least 20% of MCTD patients will evolve to another CTD (mostly SSc or SLE) within 5 years following an MCTD diagnosis and all MCTD patients are at risk of organ involvement such as oesophageal dysmotility, ILD and pulmonary hypertension (PH) [2].

Despite a supposed good prognosis and an excellent corticosteroid response, the quality of life of MCTD patients is impaired [3] and mortality ranges from 8 to 36% and is clearly linked to the occurrence of pulmonary arterial hypertension (PAH). PAH prevalence in patients with MCTD ranges from 3.4% in Hungary [4] to 43% in Japan [5] and is associated with high mortality rates (25% in Norway after 6 years, 41% in Hungary after 15 years) [6, 7]. In the Hungarian cohort of 280 MCTD patients, PAH associated with MCTD (MCTDPAH) is thus considered the first cause of death [7]. Limited data are available regarding MCTD-PAH and it must be pointed out that very few studies have reported only patients with right heart catheterization (RHC)-confirmed PAH [4, 8–10].

In order to further characterize MCTD-PAH in patients with RHC-confirmed PAH, we performed a national multicentre retrospective study taking advantage of both the national registry for MCTD and the national French Pulmonary Hypertension Registry (FPHR).

Patients and methods

Study design

We performed a retrospective multicentre cohort study in France of MCTD-PAH patients enrolled in the FPHR between January 1992 and December 2021.

Objectives of the study

The objectives of our study were to describe MCTD characteristics and PAH parameters in patients with RHC confirmed MCTD-PAH, compare patients with MCTD with or without PAH, seek factors associated with PAH in MCTD patients, compare PAH parameters of MCTD-PAH patients with SLE-PAH or SSc-PAH patients and seek associated factors of 10-year survival in MCTD-PAH patients.

Inclusion criteria

Patients with MCTD-PAH were identified through the FPHR. All adult patients enrolled in the FPHR between January 1992 and December 2021 with an MCTD diagnosis were eligible. Inclusion required a baseline RHC confirming the diagnosis of PAH and a definite diagnosis of MCTD. Thus only patients who fulfilled at least one of the four MCTD classifications (Sharp, Kasukawa, Alarcon-Segovia or Kahn [11–14]) were included in the study and PAH was defined according to the 2015 European guidelines: mean pulmonary arterial pressure (mPAP) ≥ 25 mm, mean pulmonary arterial wedge pressure (PAWP) ≤ 15 mm and pulmonary vascular resistance (PVR) > 3 Wood units (WU) [15].

Patients with MCTD-PAH were first compared with age and sex-matched MCTD patients without PAH included in the French national registry for MCTD (which included 187 patients at the time of the study) and then in patients with PAH and SSc and SLE matched on sex, age and date of PAH diagnosis enrolled in the FPHR after 2006.

Data collection

The following data were collected: demographics, tobacco exposure, date of MCTD diagnosis and clinical and biological findings (including immunological data) at MCTD onset. Regarding PAH data, the date of PAH diagnosis, New York Heart Association (NYHA) functional class, brain natriuretic peptide level, pulmonary function test, 6-min walk test and RHC results at PAH onset, as well as treatment strategy [including corticosteroids use, immunosuppressant drugs (ISDs) and PAH drugs], were recorded.

Ethical approval

This study complied with the Declaration of Helsinki. Participants gave written informed consent and anonymized data were compiled according to French regulations regarding clinical non-interventional research and the French organization dedicated to privacy, technology and civil rights in France [Commission Nationale de l'Informatique et des Libertés (CNIL)]. CNIL committee approval for collecting and analysing these data was given on 24 May 2003 (no. 842063).

According to French regulations, specific approval for this study was not mandatory.

Statistical analysis

Statistical analyses were performed using Stata/MP 13.0 (StataCorp, College Station, TX, USA). Results were expressed as frequencies and percentages for binary and categorical variables and as median and interquartile range (IQR) for continuous data. Continuous variables were compared using the t-test or Kruskal–Wallis test and categorical variables using Fisher's exact or chi-squared test. Stepwise multiple logistic regression analyses were used to assess independent associations between MCTD characteristics (including demographic, tobacco exposure, clinical and biological at disease presentation data) and MCTD-PAH occurrence or between MCTD-PAH characteristics (including demographic, tobacco exposure, clinical and biological at disease presentation and treatment strategy data) and survival based on the results of univariate analyses ($P < 0.1$) and clinical significances. Survival rates over time were plotted by the Kaplan–Meier method and compared using the log rank test.

Table 1. Characteristics of MCTD patients with and without PAH

| Characteristics | MCTD-PAH (n = 36) | MCTD controls (n = 36) | P-value |
|---|-------------------|------------------------|---------|
| Female, n (%) | 34 (94) | 34 (94) | NS |
| Age at MCTD onset, years, median (IQR) | 40 (31–48) | 39 (28–49) | NS |
| Disease duration at PAH onset, years, median (IQR) | 2 (0–6) | – | – |
| Weight, kg, median (IQR) | 56 (49–63) | 61 (54–68) | NS |
| Tobacco exposure, n (%) | 8 (22) | 6 (17) | NS |
| Clinical findings at the diagnosis of MCTD, n (%) | | | |
| RP | 32 (89) | 35 (97) | NS |
| Puffy fingers or sclerodactyly | 19 (53) | 15 (42) | NS |
| Swollen hands | 12 (33) | 6 (17) | NS |
| Malar rash | 3 (8) | 2 (6) | – |
| Pericarditis | 11 (31) | 0 (0) | <0.001 |
| Pleuritis | 0 (0) | 0 (0) | – |
| Polyarthritis | 19 (53) | 30 (83) | <0.05 |
| Alopecia | 3 (8) | 5 (14) | NS |
| Trigeminal neuralgia | 0 (0) | 1 (3) | – |
| ILD | 13 (36) | 2 (6) | <0.01 |
| Oesophageal dysmotility or dilatation | 6 (17) | 6 (17) | NS |
| Myositis | 11 (31) | 10 (28) | NS |
| Biological findings at the diagnosis of MCTD, n (%) | | | |
| Anaemia | 5 (14) | 1 (3) | – |
| Leukopenia | 3 (9) | 4 (11) | NS |
| Thrombocytopenia | 4 (11) | 0 (0) | – |
| Immunological findings, n (%) | | | |
| ANA | 35 (97) | 36 (100) | NS |
| Anti-U1-RNP antibodies | 36 (100) | 34 (94) | NS |
| Anti-dsDNA antibodies | 7 (19) | 2 (6) | NS |
| Anti-Sm antibodies | 11 (31) | 4 (11) | NS |
| Hypocomplementemia | 6 (17) | 4 (11) | NS |
| Anti-SSA antibodies | 10 (28) | 8 (22) | NS |
| Anti-Scl70 antibodies | 2 (6) | 0 (0) | – |
| Anti-centromere antibodies | 1 (3) | 0 (0) | – |
| RF positive | 7 (19) | 6 (17) | NS |
| Hypergammaglobulinemia | 15 (42) | 16 (44) | NS |

NS: not significant.

Table 2. Factors associated with PAH/PH in MCTD

| Characteristics | Odds ratio | Z-score | 95% CI | P-value |
|--------------------|------------|----------------------------|--------------|---------|
| Weight | 1.05 | 1.49 | 0.98, 1.12 | 0.14 |
| Tobacco exposure | 1.63 | 0.45 | 0.19, 14.00 | 0.65 |
| Swollen hands | 8.98 | 1.45 | 0.46, 174.72 | 0.14 |
| Pericarditis | | Predicts success perfectly | | |
| Polyarthritis | 0.08 | – 2.38 | 0.01, 0.65 | <0.05 |
| Thrombocytopenia | | Predicts success perfectly | | |
| ILD | 24.79 | 2.57 | 2.13, 287.97 | <0.05 |
| Anti-Sm antibodies | 11.33 | 2.12 | 1.19, 107.41 | <0.05 |

Results

Clinical and immunological findings

Thirty-six patients with a confirmed diagnosis of MCTDPAH were included in the study ([Supplementary Fig. S1](#), available at Rheumatology online). Baseline characteristics are detailed in [Table 1](#). Thirty-four (94%) were female and MCTD was diagnosed at a median age of 40 years (IQR 31–48). At baseline, RP, puffy fingers or sclerodactyly and polyarthritits were the main symptoms in 89%, 53% and 53% patients, respectively. Polyclonal hypergammaglobulinemia was found in 15 (42%) patients. Anti-U1-snRNP antibodies were detected in all patients (100%), whereas anti-Sm and anti-SSA antibodies were detected in 11 (31%) and 10 (28%) patients, respectively.

When compared with age- and sex-matched MCTD patients, patients with MCTD-PAH more often had pericarditis [11 (31%) vs 0 (0%); $P<0.001$] and ILD [13 (36%) vs 2 (6%); $P<0.01$] but less often had polyarthritits [19 (53%) vs 30 (83%); $P<0.05$]. Although it did not reach statistical significance, anti-Sm antibodies were more frequently detected in MCTD-PAH patients than in MCTD patients [11 (31%) vs 4 (11%)]. Multivariate analysis revealed that pericarditis, thrombocytopenia, ILD and anti-Sm antibodies were factors significantly associated with PAH/PH in MCTD patients ([Table 2](#)). When the analysis was restricted to MCTD patients without ILD, multivariate analysis revealed that pericarditis and thrombocytopenia were factors significantly associated with PAH ([Supplementary Table S1](#), available at Rheumatology online).

PAH and haemodynamic findings

PAH presentation was severe in the 36 MCTD-PAH patients ([Supplementary Table S2](#), available at Rheumatology online). Twenty-two (61%) patients were in NYHA functional class III (58%) or IV (3%) and the median 6-min walk distance was 371m (IQR 272–413). The median mPAP, PAWP and PVR were 40mm (IQR 34–49), 6mm (IQR 4–9) and 6.3WU (IQR 5.1–11.0), respectively. The median cardiac output and index were 4.9 L/min (IQR 3.7–5.7) and 3.1 L/min/m² (IQR 2.3–3.7), respectively.

Pulmonary function tests (PFTs) showed that MCTD-PAH patients had median predicted diffusing capacity for carbon monoxide (DLCO) and forced vital capacity (FVC) values of 56% (IQR 43–66) and 69% (IQR 54–92), respectively. When compared with patients with ILD, patients without ILD had a shorter disease duration [0 years (IQR 0–5) vs 6 (2–8); $P<0.01$] and a larger total lung capacity [99% (IQR 80–104) vs 58 (46–73); $P<0.05$] but did not differ otherwise ([Supplementary Table S2](#), available at Rheumatology online). When compared with PAH patients with SSc or SLE, there was no difference in PAH clinical or biological parameters, PFT results and RHC findings between MCTD-PAH patients and matched controls ([Table 3](#)).

Treatment

MCTD-PAH treatment consisted of PAH-specific therapy in 22 (61%) patients, corticosteroids in 19 (53%) patients and/ or ISDs in 20 (55%) patients. PAH-specific therapy was mainly given as a monotherapy of endothelin receptor antagonist [ERA; given in 14 (39%) patients], whereas dual PAH specific therapy or triple PAH-specific therapy was only given to 3 (8%) and 2 (6%) patients, respectively. Overall, ERA was given to 19 (50%)

patients, phosphodiesterase type 5 inhibitor (PDE5i) was given to 7 (19%) and prostacyclin analogues (PCAs) were given to 3 (8%) patients. CYC was the most common ISD used in MCTD-PAH, given in 19 (53%) patients, followed by mycophenolate mofetil in 6 (17%) patients.

Survival

Within a median follow-up of 9 years (IQR 2–11), 17 (47%) patients with MCTD-PAH died. The median age of death was 50 years (IQR 38–65) and the median time to death following an MCTD-PAH diagnosis was 3 years (IQR 1–8). Causes of death were known for nine patients and included three sudden deaths, three deaths following right heart failure, one cardiogenic shock due to atrial flutter, one sepsis shock and one digestive haemorrhage. The estimated survival rates at 1, 5 and 10 years following a PAH diagnosis were 83%, 67% and 56%, respectively. Of note, when compared with those who did not, MCTD-PAH patients who survived were more often treated with corticosteroids [13 (68%) vs 6 (35%); $P < 0.05$] and there was no significant difference with regards to CYC use [10 (53%) vs 9 (52%)]. In patients who survived, median changes in mPAP and PVR were -9.5 mmHg (CI $-17, -4.75$), 0.1 L/min/m² (CI $-0.41, -0.82$) and -3 WU (CI $-6, -0.5$), respectively.

When comparing 10-year survival of MCTD patients with and without PAH, Kaplan–Meier curves showed that MCTDPAH patients had a statistically significant worse survival than MCTD patients without PAH ($P < 0.0001$; Fig. 1A). When compared with matched controls with SLE- or SSc- PAH, Kaplan–Meier curves showed that MCTD-PAH had a similar 10-year survival ($P = 0.92$; Fig. 1B).

Multivariate analysis revealed that tobacco exposure was an independent factor associated with survival in MCTD-PAH patients (Table 4). Kaplan–Meier curves confirmed that smoker MCTD-PAH patients had a worse survival than non-smoker MCTD-PAH patients ($P < 0.05$; Fig. 1C) and did not show any difference according to the presence of ILD ($P = 0.21$; Fig. 1D).

Table 3. Haemodynamic characteristics of MCTD-PAH patients matched with SLE-PAH and SSc-PAH patients

| Characteristics | MCTD (n = 19) | SLE (n = 19) | SSc (n = 19) | P-value |
|---|----------------|---------------|---------------|---------|
| NYHA I–II, n (%) | 7 (37) | 6 (32) | 7 (37) | NS |
| NYHA III–IV, n (%) | 12 (63) | 13 (68) | 12 (63) | NS |
| BNP, pg/mL | 270 (116–1298) | 90 (69–134) | 83 (46–210) | NS |
| PaO ₂ , mmHg | 78 (70–98) | 77 (71–89) | 85 (72–103) | NS |
| PaCO ₂ , mmHg | 33 (31–35) | 36 (30–40) | 34 (32–38) | NS |
| PaO ₂ + PaCO ₂ , mmHg | 111 (101–134) | 111 (103–122) | 110 (44–130) | NS |
| 6MWD | | | | |
| Distance, m | 385 (260–450) | 354 (272–412) | 360 (318–446) | NS |
| SaO ₂ end of 6MWD, % | 92 (86–96) | 93 (89–96) | 93 (87–96) | NS |
| PFTs | | | | |
| DLCO, % of predicted | 52 (43–60) | 55 (36–60) | 38 (35–44) | NS |
| FVC, % of predicted | 69 (54–92) | 76 (58–97) | 75 (61–85) | NS |
| FVC/DLCO | 1.3 (1.1–1.4) | 1.5 (1.3–1.9) | 1.3 (1.1–1.6) | NS |
| TLC, % of predicted | 88 (70–101) | 91 (77–95) | 75 (62–85) | NS |
| FEV1, % of predicted | 70 (58–87) | 74 (54–83) | 75 (63–84) | NS |
| RHC | | | | |
| Mean sPAP | 60 (53–66) | 61 (47–77) | 51 (46–62) | NS |
| Mean dPAP | 21 (19–26) | 22 (17–28) | 23 (16–26) | NS |
| Mean PAP, mmHg | 39 (33–48) | 41 (31–48) | 33 (28–40) | NS |
| PAWP, mmHg | 6 (4–9) | 9 (5–11) | 9 (8–11) | NS |
| Cardiac output, L/min | 5.3 (3.8–6.1) | 5.0 (4.0–5.6) | 5.4 (4.4–6.0) | NS |
| Cardiac index, L/min/m ² | 3.5 (2.1–3.7) | 2.9 (2.4–3.5) | 3.2 (2.6–3.5) | NS |
| PVR, WU | 7.4 (4.7–10.4) | 6.4 (4.0–8.3) | 4.6 (3.7–7.2) | NS |
| RAP, mmHg | 6 (3–8) | 6 (3–8) | 7 (5–9) | NS |

Values are presented as median (IQR) unless stated otherwise.

6MWD: 6-min walk distance; BNP: brain natriuretic peptide; dPAP: diastolic pulmonary arterial pressure; FEV1: forced expiratory volume in 1 second; RAP: right atrial pressure, sPAP: systolic pulmonary arterial pressure; TLC: total lung capacity.

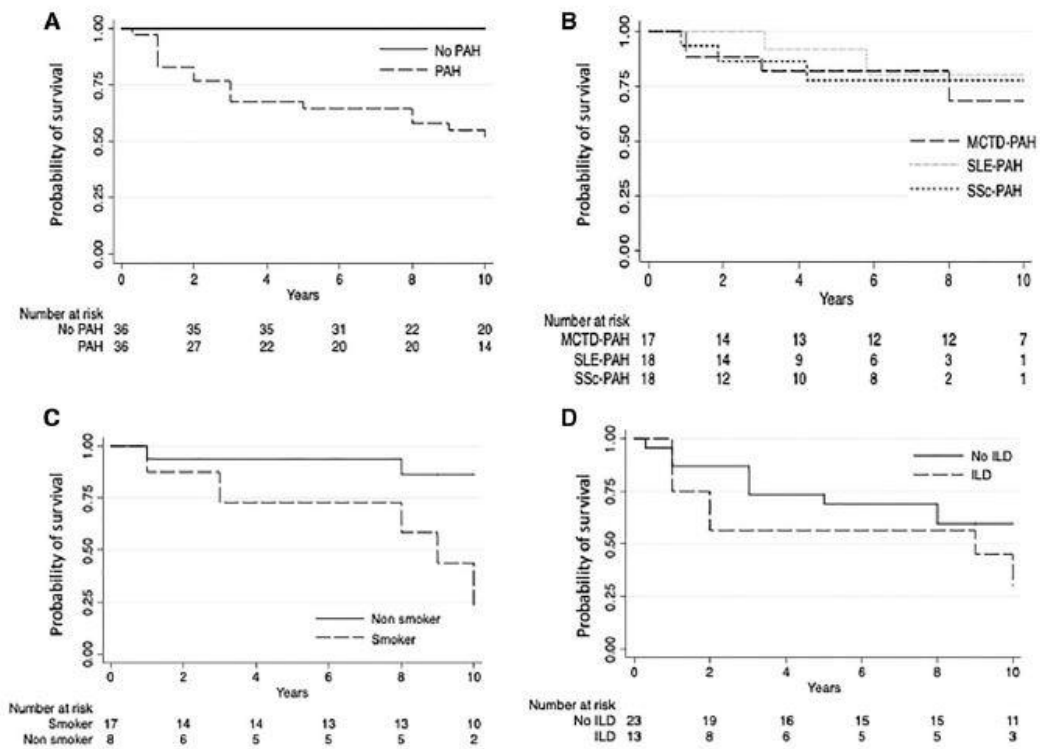


Figure 1. Probability of survival in patients with MCTD-PAH. Kaplan–Meier curves show the 10-year probability of survival in MCTD-PAH patients compared with (A) age- and sex-matched MCTD patients without PAH; (B) age-, sex- and date of diagnosis-matched SLE-PAH and SSc-PAH patients; (C) according to smoking status and (D) according to the presence of ILD.

Table 4. Multivariate analyses to determine factors independently associated with mortality in MCTD-PAH patients

| MCTD characteristics | Odds ratio | Z-score | 95% CI | P-value |
|------------------------|----------------------------|---------|-------------|---------|
| Tobacco exposure | 14.84 | 2.89 | 2.38, 92.68 | <0.05 |
| RP | Predicts failure perfectly | | | |
| Hypergammaglobulinemia | 0.90 | -1.12 | 0.14, 5.44 | 0.19 |

Discussion

PAH associated with CTD (CTD-PAH) is the second leading cause of PH [9, 16]. Although MCTD is the third leading cause of CTD-PAH following SSc and SLE [9, 16], only a few studies of MCTD-PAH are available in the literature. This led us to further study MCTD-PAH. The main findings from our study are the identification of MCTD characteristics associated with MCTD-PAH, confirmation that MCTD-PAH is associated with poor survival, the similarities between MCTDPAH and SLE- and SSc-PAH and the identification of factors associated with survival in MCTD-PAH, such as tobacco exposure.

We herein report that MCTD was diagnosed at the time of PAH diagnosis in a quarter of patients and that PAH onset occurred within 2 years after MCTD diagnosis in another quarter of patients. Furthermore, PAH presentation was severe at the time of diagnosis, as more than half of the patients presented with NYHA class III. These findings indicate that physicians who care for PH patients should continue screening for CTDs as recommended [17, 18] and emphasize the need for PAH early detection in MCTD patients.

Along this line, we sought predictive factors of PAH in MCTD patients. Interestingly, we found that ILD, thrombocytopenia, pericarditis and anti-Sm antibodies were associated with MCTD-PAH/PH. ILD is more common and has a better reported prognosis than PAH in MCTD, as its prevalence is 41% and its 5-year survival is >95% [19]. Interestingly, in the analysis of MCTD-ILD patients in Reiserter et al. [19], patients without ILD had less PAH than patients with ILD (1/ 70 vs 4/46). In this work, we did not find any haemodynamic or survival difference when we compared MCTD-PAH patients with and without ILD. This finding contrasted with the work of Chavelot et al. [20] in SSc, who reported that ILD conferred a worse prognosis on patients with SSc-PAH. Anti- Sm antibodies had previously been reported to be associated with PAH in other CTDs such as SLE. Hachulla et al. [21] reported that anti-Sm antibodies were more frequently found in SLE-PAH when compared with SLE patients without PAH (11/37 vs 14/99; $P<0.05$). Moreover, in a meta-analysis in SLE-PAH, anti-Sm antibodies had been statistically significantly reported as risk factors for SLE-PAH [22]. Of note, Jaïs et al. [8] also showed that anti-Sm antibodies were associated in both SLE-PAH and MCTD-PAH with a better response to ISD. Pericarditis had also been reported to be independently associated with the development of PH in SLE [23]. In MCTD, pericarditis is considered the main cardiac complication of the disease (prevalence ranging from 25 to 43%) [24]. Of note, Burdt et al. [25] prospectively reported 20 (43%) patients who had pericarditis at disease presentation. During follow-up, seven of them died, including five who died of PAH.

We provide one of the longest studies about MCTD-PAH survival and expanded the previous work of our group in the FPHR who reported a 3-year survival rate of 87% in seven patients with MCTD-PAH [8]. In the present work, estimated survival rates at 1, 5 and 10 years were 83%, 67% and 56%, respectively. Other studies in which the MCTD diagnosis was not necessarily reviewed reported similar survival rates. Chung et al. [9] reported a 1-year survival of 88% in 68 patients in the REVEAL registry and Condliffe et al. [10] reported 1- and 3-year survival rates of 89% and 63%, respectively, in 28 patients in the UK. Altogether, these studies and ours highlight a poor prognosis of PAH in MCTD. When compared with other CTD-PAH studies, MCTD-PAH has been reported to have a milder course and better prognosis than SSc-PAH [26]. In contrast, our work underlined that MCTD-PAH survival was similar to that of SLE- and SSc-PAH.

Our work highlighted tobacco exposure as a factor associated with modified survival in MCTD-PAH patients. Although tobacco smoke exposure has been identified once as a risk factor for PAH [27], this is the first time that it has been associated with CTD-PAH survival. Of note, in a retrospective study comparing 24 patients with pulmonary veno-occlusive disease (PVOD) with 24 randomly selected patients with idiopathic, familial or anorexigen-associated PAH but no PVOD, Montani et al. [28] reported that tobacco exposure is more frequent in PVOD than in PAH. Still, none of our patients developed documented PVOD during follow-up. Of note, probably due to the small number of patients, our work did not find any association between ISD or combination therapy and patient survival, as reported in previous studies in both PAH and MCTD-PAH [8, 29].

Our study has some limitations. First, this study is a retrospective study from a national registry. As such, antibody screening for RNP antibodies was not standardized. Second, as for every study of MCTD, the sample size of patients was small. Third, 13 patients had ILD at the time of PAH diagnosis. Although we compared them with those without ILD at the time of PAH diagnosis and although we did not find significant differences between the two groups, studies are needed to further compare PAH from ILD-PH in MCTD. Fourth, at the time of the study, the FPHR only included patients fulfilling the 2015 European Respiriolygy Society/ European Society of Cardiology guidelines. Therefore we did not include patients with MCTD-PAH fulfilling the 2022 definitions of PAH.

Despite these limitations, we believe our results derived from a large cohort of CTD-PAH patients may guide both MCTD and MCTD-PAH patient management.

To conclude, this study showed that PAH is a severe complication of MCTD, revealing MCTD in a quarter of the patients, and is associated with poor survival. It also showed that MCTD-PAH presentation and prognosis resembles that of other CTD-PAHs. Finally, it highlighted that ILD, thrombocytopenia, pericarditis and anti-Sm antibodies are associated with the occurrence of PAH/PH in MCTD patients and reinforced the need for smoking cessation in MCTD patients.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Authors' contributions

All listed authors qualify for authorship according to the following criteria: (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) Final approval of the version to be published; and (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement:

The authors have declared no conflicts of interest.

Acknowledgements

None.

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