# Clinical experience in anti-synthetase syndrome: a monocentric retrospective analytical study

**Quentin Maloir** ( q.maloir@chuliege.be )
CHU de Liège - Hôpital du Sart Tilman https://orcid.org/0000-0003-2182-5426
**Seidel Laurence**
CHU de Liege - Hopital du Sart Tilman
**Von Frenckell Christian**
CHU de Liege - Hopital du Sart Tilman
**Gester Fanny**
CHU de Liege - Hopital du Sart Tilman
**Louis Renaud**
CHU de Liege - Hopital du Sart Tilman
**Guiot Julien**
CHU de Liege - Hopital du Sart Tilman

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## Abstract

# OBJECTIVES

Anti-synthetase syndrome (ASS) is a rare auto-immune disorder combining autoantibodies and specifics clinical manifestations. One of the particularities of the ASS is the pleiomorphic radiological presentation seen at the initial work-up. Evaluating treatment response can also be challenging and requires a specific clinical, functional, biological and radiological monitoring. For these reasons is fundamental to identify specific radiological and clinical features of ASS to improve diagnosis and therapeutic approach.

# METHODS

We retrospectively studied all patients suffering from ASS in CHU of Liège from 2008 to 2019. The diagnosis of ASS was made according to ERS's criteria. We analyzed clinical features, pulmonary function test (PFT), computed tomography (CT), and longitudinal evolution with regard to their treatments.

# RESULTS

In the whole cohort of 30 patients, we identified 19 anti-JO1, 5 anti-PL12 & 6 anti-PL7. The sex-ratio is slightly in favor of male. Interestingly PL-12 syndrome was present in younger patients than those with others antibodies (mean age 39,8 vs 53,1 (JO1) & 73,3 (PL7) ($p < 0.01$)). 77% of the overall cohort exhibited specific pulmonary involvement without any significant difference with regards to the severity assessed by PFT at diagnosis. Whereas the radiological presentation was pleomorphic in the anti-JO1 syndrome, the anti-PL12 syndrome exhibited mainly ground glass opacities (GGO) as well as reticular abnormalities while those with anti-PL7 showed reticulations and bronchiectasis. The longitudinal CT analysis mainly showed up a reduction of consolidations and GGO with specific therapies.

# CONCLUSION

In our single center retrospective study, we found different profile of autoantibodies according to age and radiological appearance.

## Background

Anti-synthetase syndrome (ASS) is a rare auto-immune disorder described for the first time in 1990 [1]. Clinical expression is miscellaneous and include inflammatory myopathy (IM), interstitial lung disease (ILD), polyarthritis, mechanic’s hands, Raynaud’s Phenomenon and unexplained fever [2]. The symptomatic presentation is highly variable as well as the clinical course of the disease [3]. Pulmonary manifestations mainly drive the overall prognosis and need to be carefully assessed in all patients. Initial

presentation severity differs from asymptomatic forms to acute respiratory failure which can be responsible of an acute respiratory distress syndrome in a small number of patients [4]. A systematic blood analysis focusing on the specific antibodies assessment must be considered in the presence of any ILD. Each specific autoantibody is associated with variable clinical onset as well as the clinical evolution [5]. In the same line, treatment strategy has to be considered in an integrative way including immunological pattern, clinical onset as well as disease severity. Diagnosis of ASS associates a positive serologic testing for an anti-aminoacyl-transfer-RNA synthetase (anti-ARS) autoantibody and at least one pathognomonic clinical manifestation (Table 1) [6]. Ten specific antibodies are currently described in scientific literature. Anti-JO1 (anti-histidyl), anti-PL7 (anti-threonyl), anti-PL12 (anti-alanyl), anti-OJ (anti-isoleucyl) and anti-EJ (anti-glycyl) represent more than 90 percent of the detected ones [7]. They are now routinely tested in practice but clinician must consider that specific analysis in case of positive anti-cytoplasmic nuclear antibodies in patient suffering from ILD [8].

Table 1

Proposed criteria for myositis associated with anti-tRNA synthetase antibody according to :Connors, G. R., et al. (2010). Interstitial lung disease associated with the idiopathic inflammatory myopathies: What progress has been made in the past 35 years? Chest, 138 (6), 1464–1474. https://doi.org/10.1378/chest.10-0180

| |
|---|
| The patient must have positive tests for an anti-tRNA synthetase antibody |
| Plus one major involvement: |
| - Evidence of overt or hypomyopathic myositis (elevated CPK levels, myalgia, proximal muscular weakness, positive muscular biopsy, electromyographic triad of myositis or MRI muscular oedema) |
| - Evidence of ILD according to ATS criteria |
| - Evidence of articular involvement (symmetrical inflammatory arthralgia or overt arthritis) |
| Or two minor involvements: |
| - Unexplained, persistent fever |
| - Raynaud’s phenomenon |
| - Mechanic’s hands |

In order to assess respiratory disease severity, many tools have been developed. It is recommended to systematically evaluate pulmonary function tests (PFT), thoracic high-resolution CT scan (HRCT) as well as the potential desaturation occurring during exercises. Also blood gas analysis, bronchoalveolar lavage and exercise testing [9, 10] have been used as relevant indicators. ASS linked to interstitial lung disease is typically associated with restrictive lung function impairment and a reduced diffusing capacity of the lung for carbon monoxide (DLCO). DLCO is commonly reduced in patients with ILD, often at an earlier stage of the disease than total lung capacity (TLC) and forced vital capacity (FVC). PFT give important data to evaluate severity, as they only partially correlate with HRCT scores and pattern. In addition, PFT are more sensitive to changes upon therapy than HRCT abnormalities [11]. However, HRCT remains essential for the evaluation of lung involvement. The main CT findings with anti-ARS-ILD are areas of

ground-glass attenuation and reticulation, predominantly distributed as lower and peribronchovascular lesions, which can be compatible with fibrosing non-specific interstitial pneumonia (NSIP) pattern. A combination of patchy areas of consolidation and reticulation is frequent and may suggest the presence of myositis in subjects with ILD, especially with a subacute or an acute onset. Honeycombing (areas of small cystic spaces with thickened walls), traction bronchiectasis (bronchial dilation due to traction by fibrous tissue) and subpleural bands are less frequently observed [12].

The treatment of patients with ASS is assessed on the presence or absence of ILD, its severity and/or its initial response to treatment [13]. The available medications are restricted and corticosteroids are generally regarded as the most effective choice. The usual recommendations highlight the benefit of the association of corticosteroids at the lowest efficient dose with another adjunctive immunosuppressive agent [14]. Currently, the most commonly used treatments have based on azathioprine, mycophenolate mofetil, calcineurin inhibitors, rituximab, intravenous cyclophosphamide or intravenous immunoglobulin [15]. The choice of the immunosuppressive drug regimen and when it should be started is left to the doctor's experience. Despite these treatments, the overall mortality ratio for treated patients is significantly higher than in a standardized population of the same age and sex [16].

The aim of the present retrospective study is to analyze the ten-years clinical experience in ASS at CHU Liège (Belgium) and to confirm whether our clinical data are confident with the literature.

## Methods

Patients were selected with a retrospective data analysis focusing on positive laboratory results for an anti-ARS antibody at CHU of Liège from 1 January 2008 to 1 January 2019. The diagnosis of ASS was made according to the international recommendations of the European Respiratory Society (ERS) using major and minor criteria [17]. All clinical, imaging and spirometry data presented in this article were extracted from our electronic health record.

# Pulmonary function tests

We performed PFT in our routine respiratory laboratory of CHU of Liège. All spirometric tests performed for this study were measured using the pneumotachograph JaegerMasterlab system (Erich Jaeger GmbH, Wuzburg, Germany). The FEV1 and FVC were measured in accordance with the recommendations of ERS. The results were expressed in milliliter (mL) and percentage of predicted values (% pred). The Tiffeneau index or FEV1/FVC was expressed in percent (%). The TLC was measured by body plethysmography according to ERS recommendations. The DLCO and the report DLCO/VA were measured by the single-breath carbon monoxide gas transfer method and expressed as percentage of predicted values (% pred).

# HRCT evaluation

The initial evaluation of HRCT was firstly made by specialized thoracic radiologist followed by a specific review of each case by 2 members of the Multidisciplinary ILDs Team. CT findings were interpreted

according to the recommendations of the Fleischner Society [18], for honeycombing, reticulations, ground-glass opacities (GGO), consolidations and traction bronchiectasis. Readers also analyzed the presence of cysts, nodules, pleural or pericardial effusion and lymphadenopathy. The extent of honeycombing, reticulations, GGO and consolidations was quantified for the whole lung, using the method by Akira *et al.* [19], dividing the lungs into six zones, three for each lung (upper zone: above the level of the carina, middle zone: between level of the carina and the level of the inferior pulmonary veins, lower zone: under the level of the inferior pulmonary veins). The overall percentage of lung involvement for each sign was calculated by averaging the six lung zone values and then graded from 0 to 4, following Silva grading system [20]: 0, absent; 1, 1–4%; 2, 5–25%; 3, 26–50%; 4, > 50%. Traction bronchiectasis were graded from 0 to 3: 0, none; 1, minimal; 2, moderate; 3, severe. Grades were dichotomized in two grade categories to enable statistical analysis. Grade A included grades 0–1 and grade B included grades 2–4 for each individual sign.

# Outcome

Outcome was arbitrary defined with a multimodal approach (clinical, PFT, HRCT, blood testing) and was categorized as resolution, improvement/stabilization or deterioration. Resolution was defined as complete remission of pulmonary symptoms associated with disappearance of radiographic signs of ILD and normalization of standard PFT values. Improvement was defined as when any of the former pulmonary alterations improved without returning to normal value; according to an international consensus statement of the American Thoracic Society on idiopathic pulmonary fibrosis [21]. Changes of ≥ 10% in FVC and/or ≥ 15% in DLCO were considered significant and were used to assess improvement or deterioration.

# Statistics

Results are presented as means and standard deviation (SD) and range or as frequency tables. Comparisons between groups were done by Analysis of variance and chi-square test. Survival was represented by a Kaplan-Meier curve and groups were compared by the log-rank test. Results were considered significant at the 5% level ($P < 0.05$). Calculations were done in SAS version 9.4 and figures in R version 3.6.1.

## Results

# Clinical and biological characteristics

Subject characteristics are presented in Table 2. In the whole cohort of 30 patients, we identified 19 anti-JO1, 5 anti-PL12 and 6 anti-PL-7. The sex-ratio is slightly in favor of male, all patients being males in the Anti-PL7 group ($p = 0.021$). Interestingly PL-12 syndrome was significantly present in younger patients than those with others antibodies (mean age 39,8 vs 53 (JO1) and 73 (PL7) ($p = 0.0095$)). 77% of the overall cohort exhibited specific pulmonary involvement. The prevalence of ILD was higher in anti-PL7/PL12-positive patients compared to anti-JO1 positive patients. The first group also exhibited

rheumatological signs less frequently. We found no statistical difference between ASS patients with anti-JO1 antibody and those with anti-PL7/PL12 antibodies regarding smoking status, dermatologic sings, malignancy development or blood tests. Anti-JO1 positive patients tended to exhibit more commonly gastro-esophageal reflux disease (21% vs. 0%) although not significantly.

Table 2
Subjects characteristics

| | **All patients** (n = 30) | **Anti-JO1** (n = 19) | **Anti-PL12** (n = 5) | **Anti-PL7** (n = 6) |
|---|---|---|---|---|
| **General characteristics**: | | | | |
| Male/Female, n (%) | 16 (53) / 14 (47) | 7 (37) / 12 (63) | 3 (60) / 2 (40) | 6 (100) / 0 (0) |
| Age (years), mean ± SD [range] | 55.0 ± 19.6 [ 21–87] | 53.1 ± 19.3 [ 26–87] | 39.8 ± 14.7 [ 21–62] | 73.3 ± 7.6 [ 65–85] |
| Smokers (ever) | 11 (44) | 5 (33) | 3 (60) | 3 (60) |
| Proven deaths | 9 (30) | 6 (32) | 1 (20) | 2 (33) |
| **Biological characteristics**: | | | | |
| CRP (mg/L), median (Q1-Q3) | ND | 25 (12–91) | ND | 45 (10–47) |
| CK (UI/L), median (Q1-Q3) | ND | 528 (390–4724) | ND | 3554 (1439–5669) |
| **Clinical characteristics, n (%)**: | | | | |
| ILD | 23 (77) | 14 (74) | 4 (80) | 5 (83) |
| Myositis | 20 (67) | 15 (79) | 3 (60) | 2 (33) |
| Arthritis / Joint pain | 16 (53) | 13 (68) | 2 (40) | 1 (17) |
| Raynaud's phenomenon | 5 (17) | 3 (16) | 2 (40) | 0 (0) |
| Mechanic's hands | 7 (23) | 5 (26) | 1 (20) | 1 (17) |
| Unexplained fever | 1 (3) | 0 (0) | 1 (20) | 0 (0) |
| Dyspnea | 15 (50) | 10 (53) | 1 (20) | 4 (67) |
| Asthenia | 11 (37) | 7 (37) | 1 (20) | 3 (50) |
| Weight loss | 4 (13) | 2 (11) | 1 (20) | 1 (17) |
| Dysphagia | 1 (3) | 0 (0) | 0 (0) | 1 (17) |
| GERD | 4 (13) | 4 (21) | 0 (0) | 0 (0) |
| **Malignancy**: | 4 (13) | 3 (16) | 0 (0) | 1 (17) |

*Except where indicated, values are n (%); Q1, Q3: 1st and 3rd quartiles; CK: Creatinin Kinase; CRP: C-reactive protein; ILD: Interstitial lung disease; ND: no data; GERD: gastro-esophageal reflux disease*

# Pulmonary function tests

Twenty-six subjects (87%) had available baseline PFT. Mean data are showed in Table 3. Anti-JO1 and anti–PL7 patients presented a more restrictive pattern (TLC 73 % pred and 75% pred respectively) compared to anti–PL12 group (TLC 81%). All three anti-ARS category presented a sharp reduction in both DLCO and FVC.

Table 3
Initial pulmonary function test

| | **Anti-JO1 (n = 18)** | **Anti-PL12 (n = 3)** | **Anti-PL7 (n = 5)** |
|---|---|---|---|
| TLC, % pred | 73,3 ± 28,6 [32–122] | 81,3 ± 6,4 [74–86] | 75 ± 14,3 [58–95] |
| VC, % pred | 73,7 ± 22,3 [35–109] | 78,7 ± 5,9 [72–83] | 68,4 ± 11,4 [54–81] |
| FVC, % pred | 69,3 ± 19,6 [42–109] | 79 ± 6,9 [71–83] | 72,40 ± 13,7 [53–87] |
| $FEV_1$, % pred | 70,1 ± 18,4 [41–101] | 74,7 ± 6,8 [67–80] | 75,6 ± 11,1 [60–88] |
| $FEV_1$/FVC | 81,7 ± 10,5 [59–100] | 80,8 ± 3,7 [76,6–83] | 86,5 ± 18 [59–108] |
| DLCO, % pred | 49,7 ± 19,6 [18–82] | 58,3 ± 14,6 [42–70] | 41,8 ± 6,8 [32–50] |
| DLCO/VA, % pred | 79,9 ± 21,3 [45–121] | 78,7 ± 16,2 [60–89] | 66,6 ± 22 [41–97] |

*Data are expressed as "mean ± SD [range]"; TLC: total lung capacity; VC: vital capacity; FVC: forced vital capacity; $FEV_1$: forced expiratory volume in 1 second; DLCO: diffusing capacity of carbon monoxide; VA: alveolar volume.*

# Treatments, outcome and survival

Treatments characteristics are presented in Table 4. During the follow up, 25 out of 30 patients benefited from systemic corticosteroids (CS). CS were associated with corticoid sparing immunosuppressive agents in the majority of cases (25). The most commonly used are Methotrexate for anti-JO1-positive patients (13 cases) followed by Azathioprine (8 cases). In the anti-PL12 group, the first line of corticoid sparing agent is Azathioprine (4 cases) while there is not a predominant therapy in anti-PL7 group. CS and Methotrexate were mainly used for anti-JO1-positive patients (p = 0.039 and p = 0.041, respectively).

Table 4
Treatment characteristics

| | Anti-JO1 (n = 19) | Anti-PL12 (n = 5) | Anti-PL7 (n = 6) |
|---|---|---|---|
| Corticoids | 18 (95) | 4 (80) | 3 (50) |
| Cyclophosphamide | 2 (11) | 1 (20) | 0 (0) |
| MMF | 3 (16) | 1 (20) | 1 (17) |
| Ciclosporine | 2 (11) | 0 (0) | 0 (0) |
| Tacrolimus | 0 (0) | 0 (0) | 1 (17) |
| Rituximab | 4 (21) | 0 (0) | 0 (0) |
| MTX | 13 (68) | 1 (20) | 1 (17) |
| Azathioprine | 8 (42) | 4 (80) | 1 (17) |
| IVIG | 2 (11) | 0 (0) | 0 (0) |
| *Data are expressed as "n (%)".* | | | |
| *MMF: Mycophenolate mofetil; MTX: methotrexate; IVIG: intravenous immunoglobulins.* | | | |

After one year follow up, half of the subjects had a favorable evolution according to our criteria (see Methods - *Outcomes*). The clinical evolution of ILD after one year is summarized in Table 5. Four patients (17%) had a clinical degradation of the disease under treatment whereas six (26%) remained stable. Anti-PL7-positive subjects had proportionally the worst evolution with 50 %of them presenting a clinical deterioration. Conversely patients with anti-PL7 had better evolution with an improvement in 100 % of the cases at one year.

Table 5
Clinical evolution of ILD in each ASS after one-year follow-up

| | All patients (n = 23) | Anti-JO1 (n = 15) | Anti-PL12 (n = 4) | Anti-PL7 (n = 4) |
|---|---|---|---|---|
| **Improved** | 13 (57) | 8 (53) | 4 (100) | 1 (25) |
| **Stable** | 6 (26) | 5 (33) | 0 (0) | 1 (25) |
| **Worsened** | 4 (17) | 2 (13) | 0 (0) | 2 (50) |
| *Data are expressed as "n (%)".* | | | | |

The survival curves are presented in Fig. 1. The median survival is greater than 132 months. Survival probability at 12 months is around 86% while is around 70% for 5 years survival: there is no statistically

significant difference between the three anti-ARS autoantibody (p = 0.61). However, two subjects with anti-PL7 rapidly died after their diagnosis.

# HRCT finding

Radiological features are represented in Table 6. Radiological presentation was pleomorphic in the anti-JO1 group. Patients suffering from anti-PL12 syndrome exhibited mainly ground glass opacities (GGO) (67%) as well as reticular abnormalities (67%) while those with anti-PL7 showed reticulations (75%) and bronchiectasis (75%). The longitudinal CT analysis at 6 to 12 months mainly showed up a reduction of consolidations and GGO (36% and 54% respectively) with specific therapies (Table 7). To illustrate these findings two HRCT for an anti-PL12 and anti-PL7 patients are shown in Fig. 2.

Table 6
Initial CT findings

| Initial CT findings | All patients (n = 20) | Anti-JO1 (n = 13) | Anti-PL12 (n = 4) | Anti-PL7 (n = 4) |
|---|---|---|---|---|
| Ground glass opacities | 55 | 62 | 33 | 50 |
| Grade A (Stages 0–1) | 45 | 38 | 67 | 50 |
| Grade B (Stages 2–4) | | | | |
| Reticulations | 45 | 54 | 33 | 25 |
| Grade A (Stages 0–1) | 55 | 46 | 67 | 75 |
| Grade B (Stages 2–4) | | | | |
| Traction bronchiectasis | 62 | 62 | 100 | 25 |
| Grade A (Stages 0–1) | 38 | 38 | 0 | 75 |
| Grade B (Stages 2–4) | | | | |
| Consolidations | 75 | 69 | 100 | 75 |
| Grade A (Stages 0–1) | 25 | 31 | 0 | 25 |
| Grade B (Stages 2–4) | | | | |
| Honeycombing | 90 | 92 | 100 | 75 |
| Grade A (Stages 0–1) | 10 | 8 | 0 | 25 |
| Grade B (Stages 2–4) | | | | |
| Other | 28 | 36 | 0 | 25 |
| Nodules | 26 | 17 | 33 | 50 |
| Cysts | 0 | 0 | 0 | 0 |
| Pleural effusion | | | | |

# Data are expressed as percentage

Table 7
HRCT longitudinal analyses

| Changes in lesions between initial and follow-up CT (n = 9) | Increase or appear | No changes | Decrease | Resolved |
|---|---|---|---|---|
| GGO, n (%) | 0 | 33 | 56 | 11 |
| Reticulations, n (%) | 0 | 89 | 11 | 0 |
| Traction bronchiectasis, n (%) | 22 | 67 | 11 | 0 |
| Consolidations, n (%) | 0 | 67 | 11 | 22 |
| Honeycombing, n (%) | 0 | 89 | 0 | 11 |

*Data are expressed as percentage. The follow-up assessment was made at 6–12 months.*

# Discussion

The present study reports our experience in ASS at the University Hospital of Liege highlighting the differences between the clinical and radiological aspects. Our analysis focused on the association between anti-synthetase antibodies and ILD. Further, long-term outcomes and prognosis factors were also analyzed. The more prevalent anti-ARS auto antibodies found are anti-JO1 (59% vs 23% for PL7 and 18% for PL12). The epidemiological characteristics are partially similar than those seen in the literature [3]. Surprisingly, in our cohort we encounter significantly more male than female in the PL12 and PL7 patient groups contrary to what is generally seen for such disease [22]. The global mean age is on accordance with other cohorts. In our experience, PL7 subjects are significantly younger than the PL12 ones. Interstitial lung disease is the more frequent presentation form for all groups (70% for JO1, 87% for PL7 and 83% for PL12) and can vary in its severity at diagnosis evaluation. Early identification of ILD in ASS is fundamental for these patients as the fibro-inflammatory lung process mainly drives the mortality rate [23]. In the most severe forms, ILD can evolve into a severe respiratory failure [4]. Some patients presented an acute respiratory distress syndrome as a clinical onset. Therefore, increasing the global awareness of clinicians and especially those used to manage patients in ICU is critical for the global outcome of patients with severe ASS. Likewise, the lung involvement in PL7 and PL12 is usually described as most severe and associated with a worst prognosis than anti-JO1 but was not evidenced in this study due to the small number of patients.

Concerning the PFT, it is widely known that DLCO and to a lesser extent FVC are the most affected values in ASS. In that context, PFT has to be evaluated at diagnosis and during the follow up to reduce the risk of underestimating the severity of the disease. In our opinion, PFT must become the keystone for ASS induced ILD management and should be performed at least every 3 months during the initial follow up.

Nowadays, treatment management is still challenging in ASS [9]. There have been some recent studies comparing available immunosuppressive therapeutics and their efficacy on PFT, HRCT findings and corticosteroids sparing's efficiency [14, 24]. Our study didn't identify significant differences between immunosuppressive drug or in their regimen. Trying to find the best therapy in such diseases is a main objective for further multicentric prospective longitudinal trials. Historically, corticosteroids are the first-line therapy of idiopathic inflammatory myopathy (IIM). When corticosteroids tapering is used in monotherapy in ILD-IIM, the risk of persistence of lung disease is high. Moreover, the severity of the ILD presentation frequently requires the rapid use of aggressive immunosuppressive agents (e.g: cyclophosphamide, rituximab, etc.) [25]. Azathioprine is used as first-line therapy when an ILD is present while Mycophenolate mofetil is used by rheumatologist as first line to treat IIM without lung involvement. Other therapeutics such Tacrolimus, rituximab, intravenous immunoglobulins and Cyclophosphamide should be considered as second-line or rescue therapy in case of refractory situations like an acute respiratory distress syndrome. Those specific therapies needs to be closely monitored in their administration, and requires an expert multidisciplinary team to asses efficacy and side effects.

Considering HRCT findings, our data are in line with the literature. We found that HRCT features of ASS were mainly suggestive of NSIP at presentation. Anti-PL12 showed predominantly reticulation and GGO whereas anti-JO1 was more pleiomorphic. The most significant HRCT findings for the follow up seems to be GGO and consolidation. As expected, traction bronchectasis and honeycombing are stable during follow-up. This can be linked to the stabilization of the inflammatory process, reducing the progressive fibrosing lung disease. Nowadays, the use of specific anti-fibrotic therapies in selected patients for progressive fibrosing lung diseases is gathering considerable attention. A recently published study identifies nintedanib as effective therapy to significantly reduce FVC over the time in progressive fibrosing lung diseases [26].

# Conclusion

In conclusion, our single center retrospective study highlights some similarities with literature about clinical and radiological features of ASS. Some differences are probably due to the disease's prevalence and to the small amount of available follow-up data. Heterogeneity in the clinical course and in the response to treatment make the diagnosis, the treatment and the follow-up particularly complex. Therefore, dedicated multicentric prospective longitudinal studies are highly recommended in the specific context of ASS-ILD.

# Abbreviations

ASS: anti-synthetase syndrome

PFT: pulmonary function test

CT: computed tomography

GGO: ground glass opacities

IM: inflammatory myopathy

ILD: interstitial lung disease

Anti-ARS: anti-aminoacyl-transfer-RNA synthetase

HRCT: high-resolution CT scan

DLCO: diffusing capacity of the lung for carbon monoxide

TLC: total lung capacity

FVC: forced vital capacity

NSIP: non-specific interstitial pneumonia

ERS: European Respiratory Society

SD: standard deviation

CK: Creatinin Kinase

CRP: C-reactive protein

ND: no data;

GERD: gastro-esophageal reflux disease

CS: corticosteroids

MMF: mycophenolate mofetil;

MTX: methotrexate;

IVIG: intravenous immunoglobulins.

IIM: idiopathic inflammatory myopathy

# Declarations

### Ethics approval and consent to participate:

The protocol was approved by the ethics committee of CHU of Liège, and all subjects gave written consent before their enrollment (Belgian number : B707201422832 ; ref : 2014/302).

**Consent for publication:**

Not applicable

**Availability of data and material:**

Data could be request at the following address: q.maloir@chuliege.be

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**Authors' contributions:**

MQ was the main investigator by recovering the data and drafting the manuscript. SL performed the statistical analysis. VFC, GF and LR participated in the design of the study. GJ conceived of the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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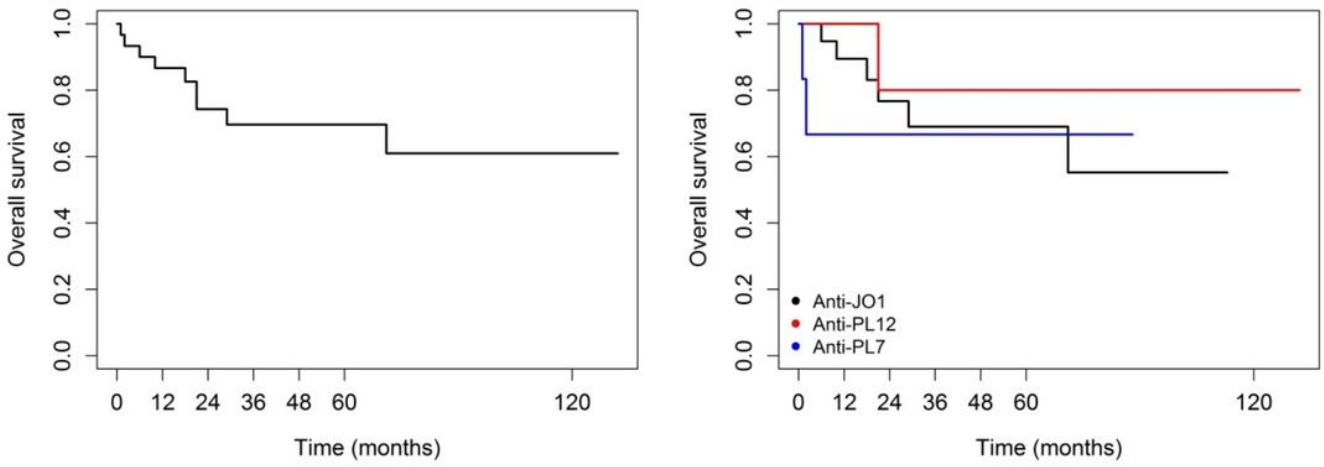
# References

1. Marguerie C, Bunn CC, Beynon HL, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA- synthetase enzymes. Quarterly Journal of Medicine. 1990;77:1019–38.
2. Solomon J, Swigris JJ, Brown KK. Myositis-related interstitial lung disease and antisynthetase syndrome. Jornal Brasileiro de Pneumologia: Publicacao Oficial Da Sociedade Brasileira de Pneumologia E Tisilogia. 2011;37(1):100–9.
3. Hervier B, Benveniste O. (2013). Clinical heterogeneity and outcomes of antisynthetase syndrome. *Current Rheumatology Reports*, *15*(8).
4. Maloir Q, Ghysen K, von Frenckell C, Louis R, Guiot J. [Acute respiratory distress revealing antisynthetase syndrome]. Rev Med Liege. 2018;73(7–8):370–5.
5. Marie I, Josse S, Decaux O, Dominique S, Diot E, Landron C, … Jouen F. Comparison of long-term outcome between anti-Jo1- and anti-PL7/PL12 positive patients with antisynthetase syndrome. Autoimmun Rev. 2012;11(10):739–45.

6. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, Du Bois RM, … Cottin V. An official European Respiratory Society/American Thoracic Society research statement: Interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46(4):976–87. https://doi.org/10.1183/13993003.00150-2015.
7. Barba T, Mainbourg S, Nasser M, Lega JC, Cottin V. Lung Diseases in Inflammatory Myopathies. Seminars in Respiratory Critical Care Medicine. 2019;40(2):255–70. https://doi.org/10.1055/s-0039-1685187.
8. Gasparotto M, Gatto M, Saccon F, Ghirardello A, Iaccarino L, Doria A. Pulmonary involvement in antisynthetase syndrome. Curr Opin Rheumatol. 2019;31(6):603–10. https://doi.org/10.1097/BOR.0000000000000663.
9. Jensen ML, Løkke A, Hilberg O, Hyldgaard C, Bendstrup E, Tran D. Clinical characteristics and outcome in patients with antisynthetase syndrome associated interstitial lung disease: a retrospective cohort study. European Clinical Respiratory Journal. 2019;6(1):1583516. https://doi.org/10.1080/20018525.2019.1583516.
10. Liu H, Xie S, Liang T, Ma L, Sun H, Dai H, Wang C. Prognostic factors of interstitial lung disease progression at sequential HRCT in anti-synthetase syndrome. Eur Radiol. 2019. https://doi.org/10.1007/s00330-019-06152-5.
11. Ciancio N, Pavone M, Torrisi SE, Vancheri A, Sambataro D, Palmucci S, … Sambataro G. Contribution of pulmonary function tests (PFTs) to the diagnosis and follow up of connective tissue diseases. Multidisciplinary Respiratory Medicine. 2019;14(1):1–11. https://doi.org/10.1186/s40248-019-0179-2.
12. Waseda Y, Johkoh T, Egashira R, Sumikawa H, Saeki K, Watanabe S, … Kasahara K. Antisynthetase syndrome: Pulmonary computed tomography findings of adult patients with antibodies to aminoacyl-tRNA synthetases. Eur J Radiol. 2016;85(8):1421–6. https://doi.org/10.1016/j.ejrad.2016.05.012.
13. Witt LJ, Curran JJ, Strek ME. The Diagnosis and Treatment of Antisynthetase Syndrome. Clinical Pulmonary Medicine. 2016;23(5):218–26. https://doi.org/10.1097/CPM.0000000000000171.
14. Barba T, Fort R, Cottin V, Provencher S, Durieu I, Jardel S, … Lega JC. Treatment of idiopathic inflammatory myositis associated interstitial lung disease: A systematic review and meta-analysis. Autoimmun Rev. 2019;18(2):113–22. https://doi.org/10.1016/j.autrev.2018.07.013.
15. Huapaya JA, Silhan L, Pinal-Fernandez I, Casal-Dominguez M, Johnson C, Albayda J, … Danoff SK. (2019). Long-Term Treatment With Azathioprine and Mycophenolate Mofetil for Myositis-Related Interstitial Lung Disease. Chest, (July), 1–11. https://doi.org/10.1016/j.chest.2019.05.023.
16. Cobo-Ibáñez T, López-Longo FJ, Joven B, Carreira PE, Muñoz-Fernández S, Maldonado-Romero V, … Nuño-Nuño L. Long-term pulmonary outcomes and mortality in idiopathic inflammatory myopathies associated with interstitial lung disease. Clin Rheumatol. 2019;38(3):803–15. https://doi.org/10.1007/s10067-018-4353-2.

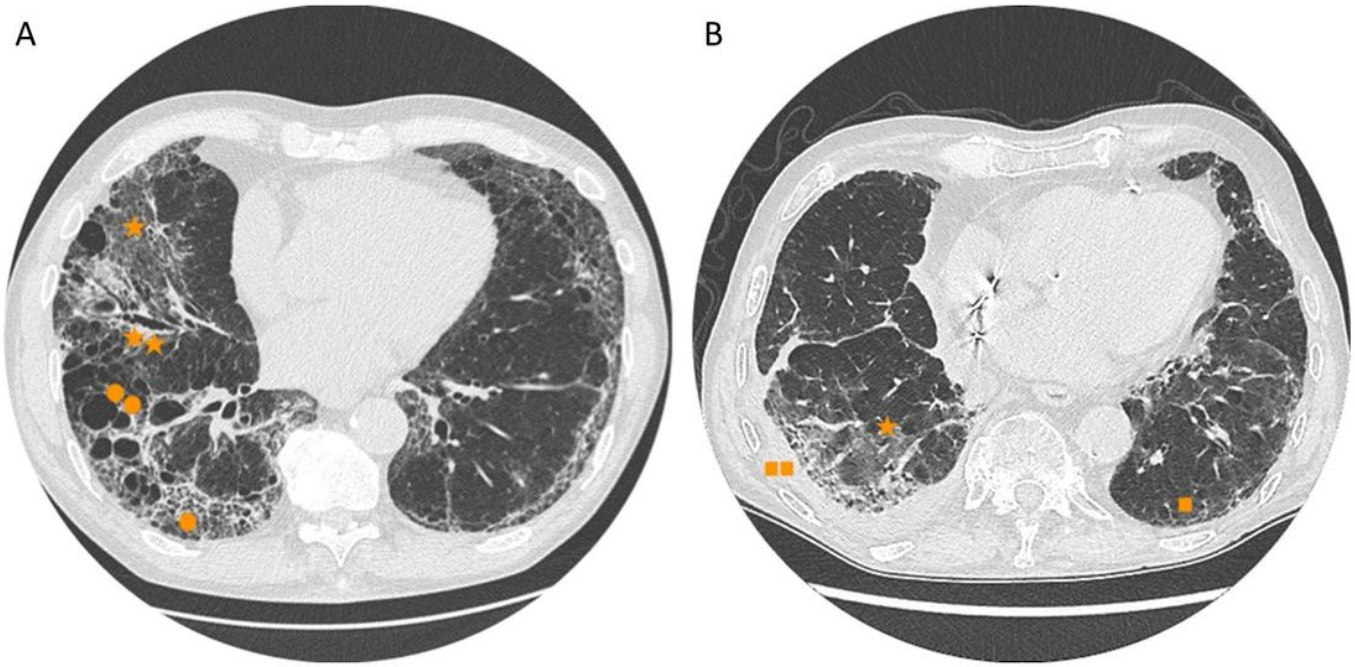
17. Lega JC, Reynaud Q, Belot A, Fabien N, Durieu I, Cottin V. Idiopathic inflammatory myopathies and the lung. European Respiratory Review. 2015;24(136):216–38. https://doi.org/10.1183/16000617.00002015.
18. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology. 2008;246(3):697–722. https://doi.org/10.1148/radiol.2462070712.
19. Akira M, Inoue Y, Arai T, Okuma T, Kawata Y. Long-term follow-up high-resolution CT findings in non-specific interstitial pneumonia. Thorax. 2011;66(1):61–5. https://doi.org/10.1136/thx.2010.140574.
20. Silva CIS, Müller NL, Hansell DM, Lee KS, Nicholson AG, Wells AU. Nonspecific Interstitial Pneumonia and Idiopathic Pulmonary Fibrosis: Changes in Pattern and Distribution of Disease over Time. Radiology. 2008;247(1):251–9. https://doi.org/10.1148/radiol.2471070369.
21. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, … Schünemann HJ. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med. 2011;183(6):788–824. https://doi.org/10.1164/rccm.2009-040GL.
22. Pinal-Fernandez I, Casal-Dominguez M, Huapaya JA, Albayda J, Paik JJ, Johnson C, … Danoff SK. A longitudinal cohort study of the anti-synthetase syndrome: Increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies. Rheumatology. 2017;56(6):999–1007. https://doi.org/10.1093/rheumatology/kex021.
23. Mejía M, Herrera-Bringas D, Pérez-Román DI, Rivero H, Mateos-Toledo H, Castorena-García P, … Rojas-Serrano J. Interstitial lung disease and myositis-specific and associated autoantibodies: Clinical manifestations, survival and the performance of the new ATS/ERS criteria for interstitial pneumonia with autoimmune features (IPAF). Respir Med. 2017;123:79–86. https://doi.org/10.1016/j.rmed.2016.12.014.
24. *Rheumatology (United Kingdom)*, *54*(8), 1420–1428. https://doi.org/10.1093/rheumatology/kev004.
25. Glaubitz S, Zeng R, Schmidt J. New insights into the treatment of myositis. Therapeutic Advances in Musculoskeletal Disease. 2020;12:1759720X1988649. https://doi.org/10.1177/1759720X19886494.
26. *New England Journal of Medicine*, *381*(18), 1718–1727. https://doi.org/10.1056/NEJMoa1908681.

# Figures




## Figure 1

ASS survival: A) overall survival of patients suffering from ASS; B): Kaplan-Meyer survival curve showing the differential survival between the 3 different ASS.




## Figure 2

Examples of HRCT findings; A) Initial HRCT from patient with anti-PL12, B) Initial HRCT from patient with anti-PL7.  : Ground glass opacities;  : Traction bronchiectasis; ●: Honeycombing; ●●: Cysts; ■: Subpleural reticulations; ■■: Pleural effusion