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ORIGINAL ARTICLE

Prevalence and clinical correlates of rheumatoid factor and anticitrullinated protein antibodies in patients with idiopathic inflammatory myopathy

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ABSTRACT

Objective As rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs) are not routinely tested in idiopathic inflammatory myositis (IIM), little is known about their prevalence and clinical implications in this patient group. In antisynthetase syndrome (ASS), presence of ACPA is reportedly associated with more severe and erosive arthritis. We aim to retrospectively determine the prevalence of RF and ACPA in a cross-sectional cohort of 121 patients diagnosed with IIM and to assess clinical associations.

Methods Serum samples from 121 patients diagnosed with polymyositis (n=30), dermatomyositis (n=41), ASS (n=37), inclusion body myositis (n=1), necrotising autoimmune myopathy (n=5) or overlap myositis (n=7) were analysed. RF was evaluated by nephelometry (Immage 800, Beckman–Coulter); anti-CCP antibodies were identified using fluoro enzyme immunoassays (Immuno-Cap 250, Thermo Fisher). Values above 40 IU/mL and 7 U/mL were considered positive for RF and ACPA, respectively.

Results The prevalence of RF and ACPA was 9.09% and 4.96%, respectively. No significant differences were observed between RF/ACPA positive versus negative patients. There was a numerical trend for RF-positive IIM patients to be older and have lower forced expiratory volume in 1 s levels.

Conclusions RF and ACPA are prevalent in IIM, although we detected a lower prevalence than reported in previous studies. Presence of these antibodies in patients with IIM patients is not clinically relevant in our cohort.

Key messages

What is already known about this subject?
► Rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs) are immunological hallmarks of rheumatoid arthritis (RA), and presence of these antibodies in RA is associated with higher disease activity and increased risk of joint destruction.
► In antisynthetase syndrome, presence of ACPA is reported to be associated with more severe and erosive arthritis.
► Little is known about the prevalence of RF and ACPA in idiopathic inflammatory myositis (IIM).

What does this study add?
► RF was found in 11 patients (9.09%) and ACPA was found in 6 patients (4.96%) out of 121 patients with IIM.
► The prevalence we detected is lower than reported in previous studies.

How might this impact on clinical practice?
► RF and ACPA are prevalent in IIM, but presence of these antibodies does not seem to be clinically relevant and therefore should not guide therapeutic decisions.

INTRODUCTION

Rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs) are antibodies that are well established as immunological hallmarks of rheumatoid arthritis (RA). RF is an immunoglobulin that reacts with the Fc portion of immunoglobulin G. As it is found in 5% of healthy individuals as part of the natural immune system, it is not specific for the diagnosis of RA. ACPAs, however, are a highly specific marker for RA, and their presence is associated with higher disease activity and more severe joint destruction.[1–4] ACPA, antibodies directed against citrullinated proteins that result from post-translational modification by the conversion of arginine to citrulline, are found in only a small percentage (less than 2%) of the general population.[4 5]

Patients with idiopathic inflammatory myositis (IIM) typically present with muscle weakness, myalgia and in case of dermatomyositis (DM) also skin involvement. Arthralgia is often present, but the articular manifestations are usually mild and non-destructive. Arthritis is more frequently seen in patients with antisynthetase syndrome (ASS), an autoimmune disease characterised by the

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association of arthritis, myositis, interstitial lung disease (ILD), Raynaud's phenomenon, mechanics' hands, fever and the presence of antiaminoacyl-tRNA synthetase antibodies (anti-ARS), of which anti-Jo1 is the most prevalent. The presence of RF and ACPA has been reported in ASS. ACPA positivity in ASS seems to be associated with more severe and erosive arthritis, often meeting the 2010 American College of Rheumatology (ACR) criteria for RA,[6] suggesting that ACPA in ASS may be considered as a marker of overlap with RA.[7 8]

Patients with arthralgia and positive RF or ACPA are referred to the rheumatology department for suspected RA. Sporadically though, the clinical presentation leads to a definite diagnosis of another connective tissue disease such as IIM. As RF and ACPA are not routinely measured when a diagnosis of IIM is suspected, little is known about the prevalence of these antibodies in this population, nor about the clinical implications of the presence hereof. In this work, we aim to retrospectively determine the prevalence of RF and ACPA in a cross-sectional cohort of 121 patients diagnosed with IIM and to assess the clinical correlates.

METHODS
Patient population
We retrospectively studied a cross-sectional cohort of 121 patients diagnosed with IIM and followed at the department of rheumatology and general internal medicine at the University Hospital of Leuven, Belgium, between 2009 and 2016. All patients included were diagnosed with DM, polymyositis (PM), inclusion body myositis or necrotising autoimmune myopathy (NAM) as judged by the clinician and based on a combination of muscle weakness, myalgia, typical dermatological findings (Gottron's papules, Gottron sign and heliotrope rash), elevated muscle enzymes and inflammatory parameters, suggestive findings on electromyography, skin and muscle biopsies and MRI. All patients fulfilled at least three out of four of the 1975 Bohan and Peter criteria.[9] Overlap myositis and necrotising autoimmune myositis were defined as suggested by Senécal et al.[10] Patients with presence of anti-ARS antibodies were included as ASS. Patients were excluded when there was no clear diagnosis of myositis or when there were no serum samples available.

Data collection
For each patient the diagnosis and demographic, clinical, biochemical and technical aspects were retrospectively retrieved. Presence of arthritis was assessed by clinical examination. ILD was defined as forced vital capacity (FVC) ≤80% with forced expiratory volume in 1 s (FEV1)/FVC ≥70% and/or total lung capacity (TLC) ≤80% and/or diffusing capacity of the lungs for carbon monoxide (DLCO) ≤80% and characteristic findings on High Resolution Computed Tomography (HRCT) such as ground glass attenuation, honeycombing, consolidation and reticular opacities.

RF and ACPA were measured on available serum samples by using respectively nephelometry (Immage 800, Beckman-Coulter) and fluoro enzyme immunoassays (Immuno-Cap 250, Thermo Fisher). If RF or ACPA were already analysed, we only repeated the analysis when the available results were measured using a different assay. Values of RF above 40 IU/mL and of ACPA above 7 U/mL were considered positive, as proposed by the manufacturer. Myositis-associated antibodies (MAAs) and myositis-specific antibodies (MSAs) were not measured per protocol for this study but retrieved from medical files when available. All available MSAs were assessed by dot immunoassay (Myositis 12 IgG DOT for BlueDiver Instrument, Alphadia, Wavre, Belgium) that detects IgG autoantibodies against Jo-1, PL-7, PL-12, EJ, SRP, Mi-2, MDA5, TIF1-γ, HMGCR, SSA/Ro52kD, SAE1/2 and NXP-2. A value above 10 arbitrary units was considered significantly positive.

Statistics
For a two-group comparison involving binary data, we used the Fisher's exact test. Comparisons involving continuous data were performed using the Mann-Whitney U test. Bonferroni correction was performed to correct for multiple testing. P values of less than 0.05 were considered significant. GraphPad Prism 7.02 was used for all the statistical analyses.

RESULTS
Patient population
One hundred and twenty-one patients diagnosed with IIM were identified (51 men, 70 women; mean age 58 years). Overall population characteristics are depicted in table 1. Most patients were diagnosed with DM (41 patients), ASS (37 patients) and PM (30 patients). Seven patients showed overlap with another systemic disease and were included as overlap myositis.

Eleven patients (9.09%) tested positive for RF, and six patients (4.96%) tested positive for ACPA. Three patients (2.48%) had positive results for both RF and ACPA, but only one patient had high titres of both antibodies (figures 1 and 1).

Details of the 14 patients who tested positive to RF and/or ACPA are summarised in table 2. Four patients were diagnosed with PM, four with DM, five with ASS and one with NAM. Ten patients had arthralgia, whereas arthritis was seen in six antibody-positive patients. Seven out of 14 patients had ILD. Based on the available documentation, five patients met the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria for the diagnosis of RA (patients 1, 5, 7, 10 and 13 in table 2).

No significant differences were observed between RF-positive and RF- negative IIM patients. We observed a trend for RF-positive IIM patients to be older (p=0.44) than RF-negative IIM patients and to more frequently carry ACPA antibodies (p=0.21) and have lower FEV1

Table 1 Population characteristics

Variable	Total (n=121)
Age (years: mean and SD)	58±14.9
Gender (male: n, %)	51 (42)
Diagnosis (n, %)	
PM	30 (25)
DM	41 (34)
NAM	5 (4)
IBM	1 (1)
ASS	37 (31)
Overlap myositis	7 (6)
Sjogren's syndrome	1
Sarcoidosis	1
Systemic sclerosis	2
Morphea	1
SLE	1
Mixed connective tissue disease	1
Disease duration (months: median and IQR)	65 (106)
Smoking (n, %)	53 (44)
MSA (≥5 AU) (n/patients checked, %)	
Mi-2	
SRP	7/92 (8)
NXP-2	2/95 (2)
MDA-5	8/92 (9)
TIF-1γ	5/92 (5)
SAE-1/2	2/92 (2)
MAA (n/patients checked, %)	
SSA/Ro-52 (≥ 5 AU)	3/92 (3)34/97 (35)
Ro-60 (≥ 7 U/mL)	4/25 (16)
U1-RNP (≥ 5 U/mL)	5/74 (7)
PM/Scl (≥ 7 U/mL)	1/82 (1)
Anti-ARS (≥5 AU) (n/patients checked, %)	
Jo-1	31/106 (29)
PL-7	2/95 (2)
PL-12	3/95 (3)
EJ	2/92 (2)
HMGCR (≥5 AU) (n/patients checked, %)	4/79 (5)

anti-ARS, anti-aminoacyl-tRNA synthetase antibodies; ASS, antisynthetase syndrome; AU, antibody units; DM, dermatomyositis; IBM, inclusion body myositis; HMGCR, anti-HMG-CoA reductase antibodies; MAA, myositis-associated antibodies; MSA, myositis-specific antibodies; NAM, necrotising autoimmune myopathy; PM, polymyositis; SLE, systemic lupus erythematosus .

values (72% vs 88%, p=0.23 (table 3)). FVC, TLC and diffusing capacity of the lungs for carbon monoxide (DLCO) levels were comparable between the RF-positive and RF-negative group. ACPA-positive patients did not differ significantly from ACPA-negative IIM patients except for a trend to more frequently be RF positive (p=0.21). There was no statistically significant difference between patients who tested positive for both RF and ACPA, and patients who tested negative for both antibodies. The presence of RF or ACPA was not significantly associated with ILD. No significant association was seen between the presence of RF or ACPA and the occurrence of arthralgia, arthritis or erosions on X-rays.

DISCUSSION

As RF and ACPA are not routinely tested in IIM, little is known about the prevalence of these antibodies in this population and their clinical implications. We tested a cross-sectional cohort of 121 patients diagnosed with IIM on the presence of RF and ACPA.

RF was found in 11 patients (9.09%). Six patients (4.96%) tested positive for ACPA, but high titres (RF >115 U/mL and ACPA >340 U/mL) were seen in only seven and two patients, respectively. These percentages are higher than the prevalence of RF and ACPA in the general population, estimated at respectively 5% and less than 2%. The prevalence of RF is estimated around 4.3%; ACPA antibodies can be found in 1.8% of healthy Caucasians.[11 12] As the mean age in our study cohort was 59 years, and considering the fact that RF-positivity increases with age leading to a prevalence of more than 10% in healthy elderly over the age of 65 years, this finding is in line with the expectations.[3 4 13]

In patients with connective tissue diseases other than RA, the prevalence of RF and ACPA is known to be higher than in healthy individuals, with prevalent ACPA in 18%–33.3% of patients with primary Sjogren's syndrome, 14%–16.6% of patients with systemic lupus erythematosus and 8.3%–13% of patients with systemic sclerosis.[13 14] In the context of IIM more specifically, Labrador-Horrillo et al[1] reported a prevalence of 13.3% ACPA positivity in 90 patients with IIM. Another report in a small group (n=21) of PM/DM patients documented presence of ACPA in 14% of patients.[14]

Taken together, the prevalence of RF and ACPA in our IIM cohort is somewhat higher than the prevalence of these antibodies in the general population but lower than the rates previously reported in other connective tissue diseases, including IIM. However, the assays used in these studies differ from the assay we used. As Coenen et al[15] suggest, the prevalence of ACPA in RA and other systemic inflammatory diseases can vary greatly using different assays. As such, firm conclusions can only be drawn when using identical assays for the measurement of ACPA and including appropriate healthy and disease control groups. This remains a clear limitation of our work.

The relevance of the presence of RF and ACPA in patients with IIM is unclear. In the aforementioned study of Labrador-Horrillo et al,[1] no statistically significant clinical correlates were found except for the higher prevalence of RF in ACPA-positive patients (p=0.043). None
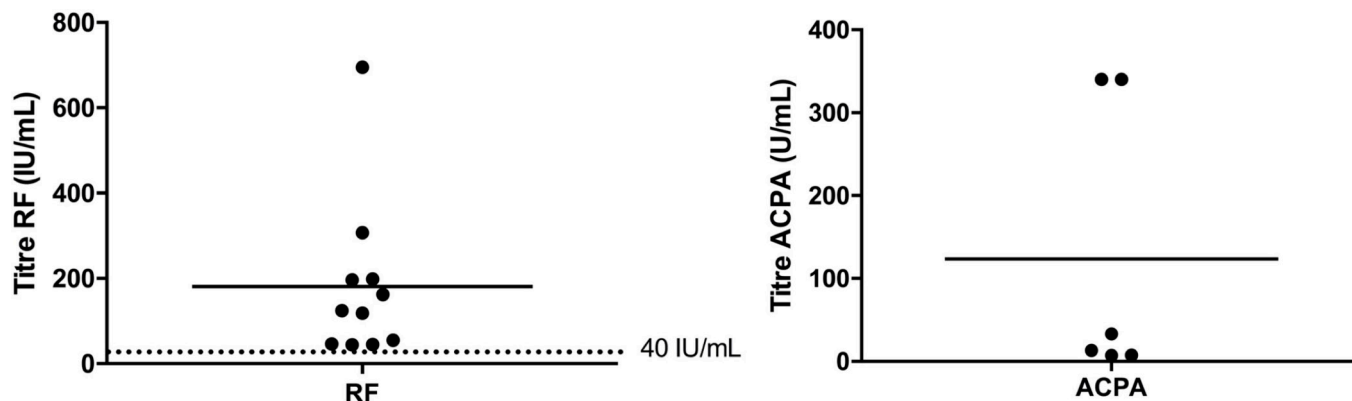
Figure 1 RF and ACPA positive titres with mean. Cut-off value of 40 IU/mL and 7.0 IU/mL, respectively. Negative samples were not depicted (RF negative n=110, ACPA negative n=115). ACPAs, anticitrullinated protein antibodies; RF, rheumatoid factor.

of the patients met the ACR classification criteria for RA, which led to the conclusion that ACPA positivity may be considered as a false-positive result without clinical significance.

We confirm the association of ACPA and RF positivity, although not reaching statistical significance in our work. RF-positive patients tended to be older than patients in the RF-negative group, which can be explained by the increasing prevalence of RF with age in the general population.

The prevalence of arthritis was similar in ACPA or RF positive and negative patients. As arthritis is a characteristic clinical manifestation of the AAS, the prevalence and clinical relevance of ACPA in ASS has been addressed before. Cavagna et al[8] found a prevalence of RF of 39% and of ACPA of 28% in a cohort of up to 58 patients with anti-Jo1 positive ASS presenting with isolated arthritis. No statistically significant association was observed between RF or ACPA positivity and the presence of radiographic erosions, but they did note a trend towards statistical significance in symmetric polyarthritis. Meyer et al,[7] retrospectively studied 17 ACPA-positive patients with ASS and compared them with 34 unselected ACPA-negative patients with ASS in a case–control study. Presence of ACPA was associated with a higher risk of arthritis and radiographic damage. As such, ACPA in ASS may be considered as a marker of overlap with RA. More recent work from the American, European Network of Antisynthetase Syndrome (AENEAS) collaborative group documented RF positivity in 15%–27% and ACPA positivity in 8%–11% of patients with ASS presenting with arthritis (n=445), with higher percentages of RF and ACPA positivity in patients where the arthritis was present from disease onset.[16]

In our cohort, we found RF or ACPA in 5/37 (13.5%) and ACPA in 3/37 patients with ASS (8.1%), but no significant association could be found between RF or ACPA positivity and the presence of arthritis or ILD. It is noteworthy that in routine clinical practice, RF and ACPA are not measured when a diagnosis of IIM is suspected and vice versa MSA/MAA are not routinely measured in case of suspected RA. As recently published, RA-like polyarthritis is a presenting feature in the majority (83%) of patients with ASS.[16] It seems highly likely that a subgroup of early arthritis patients, with suspected RA, in fact carry MSA that are missed as they are not routinely tested. As such, the lack of standardised assessment of both RF/ACPA and MSA/MAA in this group of patients, at present, precludes firm conclusions.

ACPA are thought to, at least partially, originate in the lungs, and ILD in the context of RA preferably affects RF and ACPA positive individuals.[5 17] In our study population, FEV1 values were numerically lower in RF-positive patients compared with RF-negative patients, but not reaching statistical significance. When applying the definition of ILD (FVC ≤80% with FEV1/FVC ≥70% and/or TLC ≤80% and/or DLCO ≤80% and characteristic findings on HRCT), no significant difference could be observed between RF or ACPA positive and respectively RF or ACPA negative patients. In the ACPA-positive group, smokers tended to have lower values on pulmonary function tests than non-smokers. This tendency was not seen in the ACPA-negative group. These findings are in line with the well-known association between smoking, presence of ACPA and lung disease in RA.[5 17 18] In RA, a gene–environment interaction between alleles forming the HLA shared epitope, and smoking is thought to prime the development of ACPA. Likewise, in patients with IIM, smoking appears associated with the presence of anti-Jo1 antibodies in HLA-DRB1*03-positive patients.[19] As such, smoking may effectively represent a shared risk factor for both.

There are clear limitations to this study. First, the retrospective nature of our work without standardised clinical assessment or prospective follow-up precludes any conclusions on the evolution of individual patients. Longitudinal data could shed a light on potential X-ray progression, evolution of RF/ACPA titres over time or the development of RF or ACPA positivity in individuals that are initially considered negative. Second, our study population is rather small, limiting the power of statistical analysis. Furthermore, the absence of a control group,

Table 2 Characteristics of patients positive to RF and/or ACPA

Patient	Age (years)	Gender	Diagnosis	RF (<40 IU/mL)	ACPA (<7 U/mL)	Antibody	Arthralgia	Arthritis	ILD	Smoking	Radiography
1	69*	Female	ASS (PM)	172 – 250 - 307	7.4	Jo-1 (51 U/mL)	Yes	Yes	Yes	Previous	2006 F: no erosions.
2	43	Female	DM	162	>340	ANF (1/320)	Yes	No	No	Never	/
3	71*	Male	DM, paraneoplastic	46	13	NA	Yes	No	No	Previous (46 PY)	/
4	78	Female	DM	198	0.6	ANF (1/80)	Yes	No	Yes	Never	/
5	44	Female	ASS (PM)	55	1	Jo-1 (186 U/mL) NXP-2 (58 AU) Ro-52 (>240 U/mL)	Yes	Yes	Yes	Never	/
6	77*	Female	PM	695	0.7	Ro-SSA (>240 U/mL) La-SSB (>320 U/mL)	No	No	Yes	Never	/
7	74	Female	DM	101 - 124	1.1	Mi-2 (76 AU) SSA-Ro-52 (64 AU)	Yes	Yes	No	Never	2008 F + 2014 H: no erosions.
8	67	Female	ASS	45 – 51 – 21	1	PL-12 (89 AU) SSA-Ro 52 (> 240 U/mL)	Yes	Yes	Yes	Never	2002 H+F: no erosions.
9	77*	Male	PM	196	3.6	ANF (1/80)	No	No	No	Previous	/
10	75*	Male	PM	118	0.4	SSA-Ro 52 (> 240 U/mL)	Yes	Yes	No	Previous (25 PY)	2007 H: no erosions. 2007 F: erosion right MTP1 and left MTP5.
11	68	Male	NAM	44	1	HMGCR (74 AU)	No	No	No	Previous (20 PY)	/
12	84	Female	PM	<20	33	SSA-Ro 52 (242 U/mL)	No	No	Yes	Never	/
13	49	Male	ASS (DM)	<20	<25 AU; >340 U/mL	Jo-1 (19 AU)	Yes	Yes	No	Previous (13 PY)	2015 H: no erosions.
14	56*	Male	ASS (PM)	<20	7.1	Jo-1 (116 U/mL) Ro/SSA (34 U/mL) U1-RNP (9.3 U/mL)	Yes	No	Yes	Previous (30 PY)	/

*Patients that passed away.
ACPAs, anticitrullinated protein antibodies; ANF, anti-nuclear factor; ASS, antisynthetase syndrome; DM, dermatomyositis; F, feet; H, hands; ILD, interstitial lung disease; MTP, metatarsophalangeal joint; NAM, necrotising autoimmune myopathy; PM, polymyositis; PY, pack years; RF, rheumatoid factor;.

Table 3 Comparison between RF and ACPA positive and negative patients

Variable	RF positive (n=11)	RF negative (n=110)	P value (RF)	ACPA positive (n=6)	ACPA negative (n=115)	P values (ACPA)
Age (years; mean±SEM)	68 (±3.8)	58 (±1.4)	0.44	62 (±6.3)	58 (±1.4)	1.00
Gender (male; n, %)	4 (36)	47 (43)	1.00	3 (50)	48 (42)	1.00
ACPA (≥ 7 U/mL) (n, %)	3 (27)	3 (3)	0.21			
RF (≥ 40 IU/mL) (n, %)				3 (50)	8 (7)	0.21
Gamma globulins (8–13.5 g/L; mean±SEM)	14 (±1.8)	12 (±0.5)	1.00	12 (±2.8)	12 (±0.5)	1.00
CRP at diagnosis (< 5 mg/L; mean±SEM)	53 (±18.8)	19 (±3.9)	1.00	37 (±25.6)	23 (±4.3)	1.00
ESR at diagnosis (< 15 mm/hour; mean±SEM)	53 (±11.5)	30 (±2.8)	1.00	57 (±14.2)	31 (±2.8)	1.00
CK at diagnosis (< 190 U/L; mean±SEM)	2127 (±1036)	3274 (±880)	1.00	552 (±248)	3308 (±844)	1.00
Smoking (n, %)	5 (45)	48 (48)	1.00	4 (67)	49 (47)	1.00
Dyspnoea (n, %)	8 (73)	55 (50)	1.00	4 (67)	59 (51)	1.00
FEV1 (%, mean±SEM)	72 (±5.6)	88 (±2.1)	0.23	76 (±7.8)	87 (±2.1)	1.00
FVC (%, mean±SEM)	79 (±6.4)	94 (±2.1)	0.63	83 (±5.8)	93 (±2.2)	1.00
DLCO (%, mean±SEM)	67 (±8.2)	67 (±2.1)	1.00	51 (±10.2)	68 (±2.1)	1.00
TLC (%, mean±SEM)	80 (±4.4)	90 (±1.9)	1.00	78 (±4.6)	90 (±1.8)	1.00
ILD (n, %)	5 (45)	31 (28)	1.00	3 (50)	33 (29)	1.00
Arthralgia (n, %)	8 (73)	68 (62)	1.00	5 (83)	71 (62)	1.00
Arthritis (n, %)	5 (45)	31 (28)	1.00	2 (33)	34 (30)	1.00
Erosion on RX (n=44, n, %)	1 (20)	6 (15)	1.00	0 (0)	7 (17)	1.00
MSA (n, %)	2 (18)	23 (21)	1.00	0 (0)	27 (23)	1.00
MAA (n, %)	6 (55)	33 (30)	1.00	3 (50)	36 (31)	1.00
ARS (n, %)	3 (27)	34 (31)	1.00	3 (50)	34 (30)	1.00

ACPAs, anticitrullinated protein antibodies; ARS, antiaminoacyl-tRNA synthetase antibodies; CK, creatinine kinase; CRP, C reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; MAA, myositis-associated antibodies; MSA, myositis-specific antibodies; RF, rheumatoid factor; TLC, total lung capacity.

assessing RF and ACPA positivity in healthy and disease control groups, remains a major limitation to our work.

CONCLUSION

In conclusion, this study demonstrates that RF and ACPA are prevalent in patients with IIM, but the detected prevalence is lower than the prevalence reported in previous studies in connective tissue diseases including IIM. Our results did not show a clear association between RF or ACPA positivity and specific clinical features or the occurrence of ILD or arthritis. Our results suggest that the presence of RF or ACPA in IIM may not be clinically relevant, but more studies are needed.

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