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Pulmonary manifestations of the idiopathic inflammatory myopathies in a South African population

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Background. Pulmonary complications cause significant morbidity and mortality in patients with idiopathic inflammatory myopathies (IIMs).
Objectives. To describe the frequency and spectrum of pulmonary complications in patients with IIMs in South Africa (SA).
Methods. A retrospective records review of adult patients with IIMs or clinically amyopathic dermatomyositis (CADM) presenting with respiratory complaints at a tertiary care facility in SA was performed. Clinical features, results of laboratory and pulmonary function tests (PFTs), radiological findings and treatment were recorded.
Results. Pulmonary complications were documented in 66 patients. Most patients (n=41; 62.1%) had dermatomyositis, 14 (21.2%) had polymyositis, and 3 (4.5%) had CADM. There were 8 patients with overlap syndromes. Dyspnoea and a dry cough were the most common presenting symptoms, in 52 (78.8%) and 36 (54.5%) patients, respectively. Bibasal crackles were noted in 38 patients (57.6%). Interstitial lung disease (ILD), followed by infection and pulmonary hypertension (PH), were documented in 46 (69.7%), 16 (24.2%) and 9 (13.6%) patients, respectively. Nine patients had microbiologically confirmed pulmonary tuberculosis. Patients who were anti-Jo1 antibody positive (n=16) had higher levels of acute inflammatory markers and muscle enzymes compared with the rest of the patients (p<0.0001). Dyspnoea and bibasal crackles were associated with significantly lower baseline and 12-month lung function parameters. Nonspecific interstitial pneumonia was the most common radiological pattern of ILD, present in 25 (62.5%) of the patients with ILD.
Conclusion. ILD was the most prevalent complication in this study of SA patients with IIMs. Pulmonary infections and PH were also significant contributors to morbidity. The presence of dyspnoea and crackles was predictive of lower baseline PFTs in this population.
Keywords. Interstitial lung disease, idiopathic inflammatory myopathies, autoimmune diseases, dermatomyositis, polymyositis.

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Study synopsis
What the study adds. Pulmonary complications, including interstitial lung disease (ILD) and infections, are significant contributors to morbidity and mortality in patients with idiopathic inflammatory myopathies (IIMs). There is very little research currently available to describe the spectrum of pulmonary manifestations in these patients in an African setting, a lack that this study aimed to address.
Implications of the findings. ILD was the most common pulmonary complication in patients with IIMs in this cohort. Signs and symptoms of ILD may be present before symptoms of myositis, and dyspnoea and a dry cough were shown to be predictive of reduced lung volumes. Patients with IIMs on immunosuppressive therapy in our setting are at high risk of infection, particularly tuberculosis.

Idiopathic inflammatory myopathies (IIMs) are a group of rare systemic autoimmune rheumatic disorders (SARDs) characterised by muscle inflammation, presenting clinically as proximal muscle weakness with variable extramuscular manifestations, especially skin involvement. The estimated prevalence of IIMs is 1 - 2 cases per 100 000 in the general population. IIM was initially classified by Bohan and Peter in 1975[1] into the two major variants of dermatomyositis (DM) and polymyositis (PM), but several other variants under the broad group of IIMs were described later. These include inclusion body myositis, the antisynthetase syndrome and clinically amyopathic dermatomyositis (CADM).

Pulmonary complications are reported to occur in 20 - 75% of patients with IIMs, are often associated with clinically significant morbidity and sometimes cause death. They range from acute infections, aspiration pneumonia, respiratory muscle weakness, interstitial lung disease (ILD), pneumomediastinum and pulmonary hypertension (PH) to primary lung malignancies.[2-4] Of these, ILD is often the most frequent chronic complication, documented in 27.9% of IIM patients in a recent study from a tertiary hospital in Durban, South Africa (SA).[5] Moreover, ILD in IIM is often associated with poor outcomes, with higher rates of morbidity and mortality than IIM without ILD.[6,7] Specific clinical phenotypes and autoantibody profiles of IIM that are associated with

ILD have been identified. Anti-melanoma differentiation-associated protein 5 (MDA5) antibodies are associated with rapidly progressive ILD and sometimes malignancy, and anti-aminoacyl-tRNA synthetase (ARS) antibodies with fever, Raynaud's phenomenon, mechanic's hands and ILD.[8-10] Measurement of myositis-specific antibodies (MSAs) allows for better risk stratification and prognostication and early therapeutic intervention in ILD.

Published literature on the frequency and spectrum of pulmonary complications of IIMs in Africa is sparse. The present study was undertaken to describe the demographics of patients with IIMs attending a tertiary care centre in SA, together with clinical features, laboratory results and pulmonary involvement.

Methods

A retrospective records review of adult patients with IIMs or CADM presenting with respiratory complaints to a tertiary care facility in SA between 1 January 2003 and 31 December 2019 was performed. A total of 77 patient files were identified in the respiratory clinic records, but 11 patients were excluded from the study owing to lack of evidence of respiratory complications. All patients fulfilled the Bohan and Peter criteria for IIM[1] or the Sontheimer classification criteria for CADM[11] and were ≥18 years old at symptom onset. Patients defined as having overlap myositis fulfilled the classification for IIM and had features of another SARD, i.e. scleroderma, rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M200755).

Data extracted from case records were patient demographics, respiratory signs and symptoms, laboratory results, results of pulmonary function tests (PFTs), and chest radiograph (CXR) and high-resolution computed tomography (HRCT) findings. Laboratory data included a baseline full blood count, erythrocyte sedimentation rate, C-reactive protein (CRP), aldolase, creatine kinase (CK) and aspartate transaminase (AST) levels, and HIV serology, antinuclear antibody (ANA) and anti-Jo1 antibody test results. Sputum microbiological and cytological findings and lung histological findings were documented in cases where infection or malignancy was suspected. PFTs that were documented at baseline and subsequent follow-up visits were the percentage of the predicted forced expiratory volume in the 1st second (FEV_1%pred), forced vital capacity (FVC%pred), total lung capacity (TLC%pred), residual volume (RV%pred) and lung diffusion capacity for carbon monoxide (DL_{CO}%pred), using the Third National Health and Nutrition Examination Survey (NHANES III)[12] as reference criteria with a 10% correction for races other than white.

Pulmonary artery systolic pressure, as estimated using tricuspid valve regurgitant velocity, and left ventricular ejection fraction were measured using transthoracic echocardiography. PH was defined as an estimated right ventricular systolic pressure >35 mmHg.[13]

Diagnosis of specific pulmonary complications was based on a combination of clinical features, imaging changes (CXR and HRCT findings), sputum results, PFT results, echocardiography, and rarely lung histology. HRCT ILD patterns were determined by a diagnostic radiologist and classified as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organising pneumonia (OP), diffuse alveolar damage or non-ILD changes, using characteristic imaging patterns.[14]

Statistical analysis

Descriptive statistics for continuous variables were expressed as either means (standard deviation (SD)) or medians (interquartile range), depending on whether the data were normally distributed or skewed. The two-sample independent *t*-test or Mann-Whitney test was used to compare normally distributed or skewed continuous variables, respectively. In the case of categorical variables, Pearson's χ^2 test or a two-tailed Fisher's exact test (for small sample size) was applied for frequency comparisons between groups. Statistical significance was set at $p<0.05$.

Results

Of the 77 patients with IIMs referred to the respiratory clinic for assessment, 66 had confirmed pulmonary complications (Table 1). Eleven patients with no evidence of respiratory involvement were excluded from the study. Most of the patients (*n*=54; 81.8%) were female, 14 (21.2%) had PM, 41 (62.1%) had DM, 3 (4.5%) had CADM, and 8 (12.1%) had overlap myositis (OM). Mean (SD) age at diagnosis and follow-up duration were 40.8 (14.1) years and 6.2 (6.0) years, respectively. Compared with the group with DM/CADM/OM (group 2), patients with PM (group 1) were significantly older at diagnosis (mean 48.9 v. 38.4 years, respectively; $p=0.01$). Of 55 patients in whom the sequence of muscle and respiratory symptoms was recorded, in most (*n*=33; 60.0%) muscle symptoms preceded respiratory symptoms, in 14 (25.5%) respiratory symptoms preceded muscle symptoms, and in 8 (14.5%) muscle and respiratory symptoms occurred concurrently.

Muscle weakness was present in 54 patients (81.8%) at presentation, in all the group 1 patients but only 39 (75.0%) of the group 2 patients ($p=0.04$). Gottron's papules/sign was the most common dermatological feature in group 2. The most frequent clinical pulmonary features were dyspnoea (*n*=52 patients; 78.8%), a dry cough (*n*=36; 54.5%) and basal crackles (*n*=38; 57.6%). ILD and infections accounted for most pulmonary complications, in 46 (69.7%) and 16 (24.2%) patients, respectively. There were 19 incidents of pulmonary infection in 16 patients, with 3 patients presenting with two episodes of infection. Microbiologically confirmed pulmonary TB (PTB) was documented in 9 patients, of whom only 1 had HIV co-infection. Two patients had respiratory muscle weakness. Lung biopsy was performed in 5 patients, with histopathological examination showing OP in 3 and primary lung malignancy in 2. Baseline mean CRP, white cell count (WCC) and CK were significantly higher in group 1 than in group 2 ($p=0.049$, $p=0.04$ and $p=0.002$, respectively). ANA was positive in 29/57 (51.1%) patients, anti-Jo1 in 16/47 (34.0%) and anti-Ro in 6/25 (24.0%).

The most common HRCT ILD patterns were NSIP (*n*=25/46; 54.3%) and UIP (*n*=15/46; 32.6%); the rest of the patients had OP (*n*=3/46; 6.5%), bronchiolitis obliterans (*n*=1/46; 2.2%) and unspecified ILD (*n*=2/46; 4.3%). There were no significant differences in ILD patterns between group 1 and group 2. Specific HRCT abnormalities in the 46 patients diagnosed with ILD were ground-glass attenuation in 27 (58.7%), honeycombing in 21 (45.7%) and traction bronchiectasis in 18 (39.1%).

PFTs in the 40 ILD patients with either NSIP (*n*=25) or UIP (*n*=15) showed that the overall baseline mean (SD) FEV_1%pred was 73.0 (21.3), FVC%pred 72.5 (22.1), RV%pred 80.9 (25.7), TLC%pred

Table 1. Baseline characteristics of patients with IIMs with pulmonary manifestations

Variable	All patients (*N*=66), *n* (%)*	PM (group 1) (*n*=14), n (%)*	DM/CADM/OM (group 2) (*n*=52), *n* (%)*	*p*-value
Age (years), mean (SD)	40.8 (14.4)	48.9 (12.3)	38.4 (14.2)	0.01
Female	54 (81.8)	11 (78.6)	43 (82.7)	NS
Current/ever smoker	7/62 (11.3)	3/14 (21.4)	4/48 (8.3)	NS
Sequence of symptoms				
Muscle first	33/55 (60.0)	10/12 (83.3)	23/43 (53.5)	NS
Respiratory first	14/55 (25.5)	1/12 (8.3)	13/43 (30.2)	NS
Simultaneous	8/55 (14.5)	1/12 (8.3)	5/43 (11.6)	NS
Myalgia	43 (65.1)	14 (100)	29 (55.8)	0.001
Muscle weakness	54 (81.8)	14 (100)	39 (75.0)	0.04
Heliotrope rash	13 (19.7)	0	13 (25.5)	-
'V' sign	12 (18.2)	0	12 (23.5)	-
Shawl sign	10 (15.2)	0	10 (19.6)	-
Gottron's papules	35 (53.0)	0	35 (68.6)	-
Mechanic's hands	10 (15.2)	0	10 (19.6)	-
Dyspnoea	52 (78.8)	14 (100)	38 (73.1)	NS
Dry cough	36 (54.5)	8 (57.1)	28 (53.8)	NS
Basal crackles	38 (57.6)	10 (71.4)	28 (53.8)	NS
Finger clubbing	5/65 (7.7)	2 (14.3)	3/51 (5.9)	NS
Interstitial lung disease	46 (69.7)	11 (78.6)	35 (67.3)	NS
NSIP	25/46 (54.3)	5 (35.7)	20 (38.5)	NS
UIP	15/46 (32.6)	4 (28.6)	11 (21.1)	NS
OP	3/46 (6.5)	1 (7.1)	2 (3.8)	NS
Pulmonary hypertension	9/17 (52.9)	5/5 (100)	4/12 (33.3)	NS
Any infection†	16 (24.2)	5 (33.3)	11 (21.6)	NS
Bacterial pneumonia	10 (15.2)	3 (21.4)	7 (13.7)	NS
PTB	9 (13.6)	2 (13.3)	7 (13.7)	NS
Bronchogenic adenocarcinoma	2 (3.0)	0	2 (4.3)	NS
CK (IU/L), mean (SD)	2 351 (3 188)	5 553.4 (4 263.6)	1 860.3 (2 957.3)	0.0004
ANA positive	29/57 (50.8)	5/13 (38.5)	24/44 (54.5)	NS
Anti-Jo1	16/47 (34.0)	8/9 (88.9)	8/38 (21.1)	0.0001
Lost to follow-up	13 (19.7)	3 (20.0)	10 (19.6)	NS

IIMs = idiopathic inflammatory myopathies; PM = polymyositis; DM = dermatomyositis; CADM = clinically amyopathic dermatomyositis; OM = overlap myositis; SD = standard deviation; NS = not significant; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia; OP = organising pneumonia; PTB = pulmonary tuberculosis; CK = creatine kinase; ANA = antinuclear antibody.

*Except where otherwise indicated.

†Some patients had more than one type of infection.

69.7 (19.5), DL_{CO}%pred 62.8 (23.2) and FEV_1/FVC ratio 73.2 (24.9). Other than patients with UIP being significantly older than those with NSIP (mean (SD) 46.8 (14.1) years v. 37.6 (11.5) years, respectively; p=0.03) and having a higher baseline CRP (51.1 (61.4) v. 16.5 (17.7) mg/L, respectively; p=0.04), there were no significant differences in clinical characteristics or baseline PFT results between patients with UIP and NSIP.

As shown in Table 2 and Fig. 1, in the 40 patients with either UIP or NSIP, dyspnoea was associated with significantly lower mean baseline FEV_1%pred, FVC%pred and DL_{CO}%pred (p=0.01 for all) and TLC%pred (p=0.02) compared with patients without dyspnoea. Similarly, patients reporting a dry cough had significantly lower baseline mean FEV_1%pred, FVC%pred and DL_{CO}%pred (p=0.02, 0.048 and 0.003, respectively) compared with those without a cough (Fig. 2). Audible bibasal crackles were associated with significantly lower RV%pred and DL_{CO}%pred (p=0.02 and p=0.0005, respectively) (Fig. 3). In addition, bibasal crackles were more common in patients with UIP than in those with NSIP (odds ratio (95% confidence interval) 5.1 (1.15 - 22.6); p=0.03).

Fifteen of 16 patients who tested positive for anti-Jo1 antibodies had ILD, and most (n=10) had PM. Anti-Jo1-positive patients had significantly higher mean baseline CRP, WCC, CK, aldolase and AST (Table 3) and a lower mean 12-month DL_{CO}%pred.

Thirteen of the 66 patients overall (19.7%), but only 3 of the 46 patients with ILD (6.5%), were lost to follow-up at 12 months. Mortality data were only available for 1 patient; however, 53 patients were known to be alive at the time of the final data

Table 2. Significant association of signs and symptoms with PFTs in patients with IIMs with either NSIP or UIP (*N*=40)

Variable (baseline)	Dyspnoea present (*n*=32; 80.0%)	Dyspnoea absent (*n*=8; 20.0%)	*p*-value
FEV_1%pred, mean (SD)	67.0 (16.3)	102.0 (27.6)	0.01
FVC%pred, mean (SD)	67.0 (16.2)	100.0 (26.7)	0.01
TLC%pred, mean (SD)	64.0 (13.7)	88.5 (22.6)	0.02
DL_{CO}%pred, mean (SD)	58.5 (14.8)	89.0 (25.2)	0.01
	Dry cough present (*n*=25; 62.5%)	**Dry cough absent (*n*=15; 37.5%)**	
FEV_1%pred, mean (SD)	66.5 (19.4)	83.2 (20.8)	0.02
FVC%pred, mean (SD)	66.7 (20.8)	81.6 (21.7)	0.048
DLCO%pred, mean (SD)	54.1 (21.2)	78.2 (18.5)	0.003
	Crackles present (*n*=29; 72.5%)	**Crackles absent (*n*=11, 27.5%)**	
RV%pred, mean (SD)	73.7 (23.4)	96.9 (24.4)	0.02
DL_{CO}%pred, mean (SD)	54.8 (18.0)	84.2 (22.5)	0.0005

PFTs = pulmonary function tests; IIMs = idiopathic inflammatory myopathies; NSIP = nonspecific interstitial pneumonia; UIP usual interstitial pneumonia; FEV_1%pred = percentage of the predicted forced expiratory volume in the 1st second; FVC%pred = percentage of the predicted forced vital capacity; TLC%pred = percentage of the predicted total lung capacity; DL_{CO}%pred = percentage of the predicted lung diffusion capacity for carbon monoxide; RV%pred = percentage of the predicted residual volume.

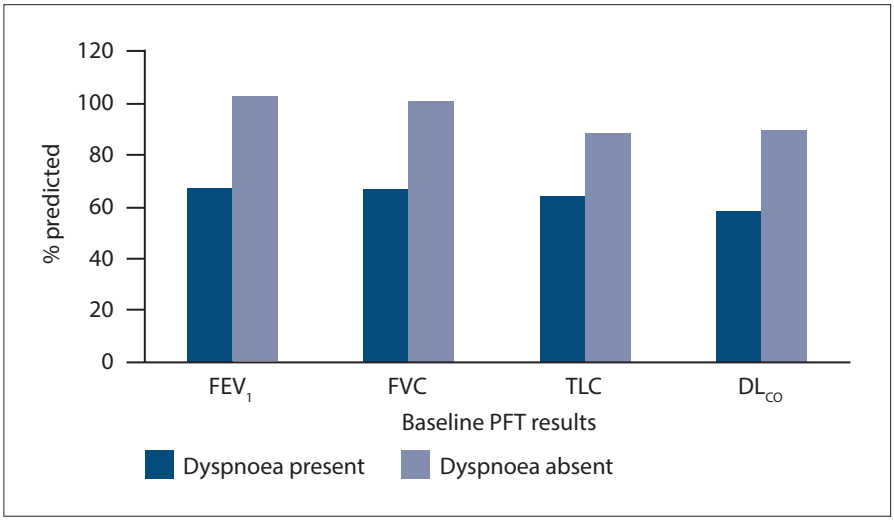


Fig. 1. Association of lung volumes with presence or absence of dyspnoea. (FEV_1 = forced expiratory volume in the 1st second; FVC = forced vital capacity; TLC = total lung capacity; DL_{CO} = lung diffusion capacity for carbon monoxide; PFT = pulmonary function test.)

collection.

Discussion

Pulmonary complications are increasingly being recognised as important causes of morbidity and mortality in patients with IIMs.[15] In this study of patients with IIMs referred to a respiratory service in SA, the commonest pulmonary complications were ILD and infections.

Consistent with previous studies,[15-18] ILD was the most common pulmonary complication in the present study, documented in just over two-thirds of IIM patients. Moreover, as in other studies, NSIP was the predominant subtype of IIM-associated ILD, followed by UIP.[2,3,16,19] Patients with UIP in the present study were on average a decade older than those with NSIP, consistent with the ILD literature showing that UIP is mainly a disease of the elderly.[20] We observed no difference in baseline PFT results between the two subgroups, but UIP in association with connective tissue disease is known to be less responsive to corticosteroids and immunosuppressive agents and to have a worse prognosis than NSIP or OP.[21,22]

Our findings underscore the importance of clinical symptoms and signs in relation to disease severity in IIM-associated ILD. We found that patients with dyspnoea and/or a dry cough had worse PFT results at baseline than those without, specifically with regard to FEV_1%pred, FVC%pred and DL_{CO}%pred. Bibasal crackles in the present study were associated with significantly lower baseline RV%pred and DL_{CO}%pred. Fine Velcro basal crackles on auscultation are an early sensitive and specific sign of IPF.[23] In the present study, patients with UIP were five times more likely to have basal crackles compared with patients with NSIP. Our finding that pulmonary symptoms were evident before muscle symptoms in 25.5% of patients is at odds with earlier studies, in which pulmonary and muscle symptoms were generally found to present simultaneously.[3,4,16] This may in part be due to increased awareness and recognition of ILD, especially NSIP, as the initial manifestation of IIM, and greater access to HRCT imaging.

There are now several MSAs that have been shown to be associated with specific clinical phenotypes. Of these, anti-Jo1 (histidyl-tRNA synthetase) antibody is the commonest anti-tRNA synthetase antibody associated with the antisynthetase syndrome phenotype with variable clinical features of Raynaud's phenomenon, fever, inflammatory arthritis, mechanic's hands and ILD.[8,24] Until very recently, the anti-Jo1 antibody test was the only MSA test available at our institution. In the subgroup of patients who were tested for anti-Jo1 antibodies, they were significantly more common in patients with PM rather than the other clinical phenotypes and were associated with significantly higher baseline CRP, total WCC, CK, aldolase and AST.

PTB was common in our study, found in 9 patients, with only one patient being co-infected with HIV. All the patients were on

corticosteroids and immunosuppressants, emphasising the risks that the underlying disease and drugs pose in endemic areas. In addition to the risks of immunosuppression, a recent study in India suggests that IIM may be an independent risk factor for the development of PTB, with higher rates of infection compared with patients with SLE on similar immunosuppressive doses.[25] More research is needed to elucidate this risk further.

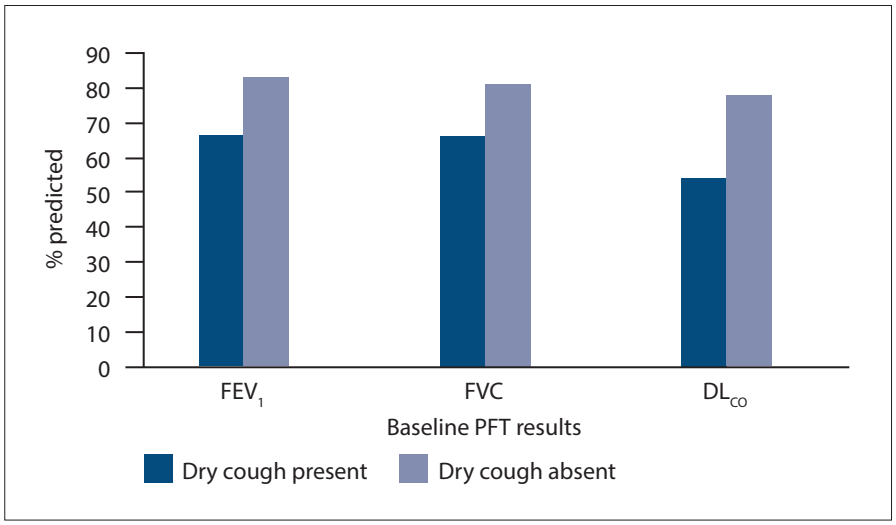


Fig. 2. Association of lung volumes with presence or absence of dry cough. (FEV_1 = forced expiratory volume in the 1st second; FVC = forced vital capacity; DL_{CO} = lung diffusion capacity for carbon monoxide; PFT = pulmonary function test.)

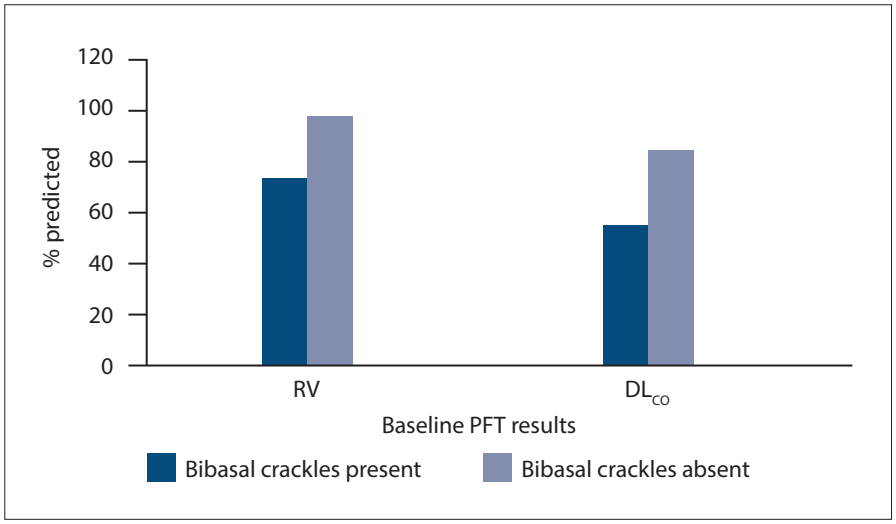


Fig. 3. Association of lung volumes with presence or absence of bibasal crackles. (RV = residual volume; DL_{CO} = lung diffusion capacity for carbon monoxide; PFT = pulmonary function test.)

Malignancy was not a common finding in our patients, despite the well-described association of malignancy with DM and PM.[26] This result may be accounted for by the younger age of our cohort, as well as the relatively short mean follow-up time of 6.2 years.

There are limitations to our study. Firstly, the retrospective study design resulted in inconsistencies in data parameters that were available for analysis, with missing data in some files and no mortality data. The study was conducted in a single centre and may therefore not be widely applicable to the population as a whole. In addition, some selection bias may be present, as the clinical data were based on case records of outpatients attending the respiratory and/or rheumatology clinics only, with no clinical data from neurology and general medicine.

Another limitation is the lack of right heart catheterisation to confirm the diagnosis of PH in our patients. The gold standard for the diagnosis of PH is a pulmonary artery systolic pressure >20 mmHg at rest on right heart catheterisation.[13] However, right heart catheterisation is invasive and not readily available in our setting. We therefore used estimated pulmonary artery systolic pressure derived from tricuspid valve regurgitant velocity on a transthoracic echocardiogram as a marker of PH.[13]

Laboratory assays for many myositis-associated and myositis-specific autoantibodies that have been shown to be associated with ILD are not currently readily available in SA, which limits the ability to determine the risk of development and progression of ILD in patients with these autoantibody profiles. Anti-Jo1 is the only antisynthetase antibody that can currently be tested for in our setting.

Conclusion

Respiratory complications are an important cause of morbidity in patients with IIMs.

Table 3. Significant laboratory associations with anti-Jo1 antibody status in patients with IIMs (*N*=47)

Variable	Anti-Jo1 positive (*n*=16)	Anti-Jo1 negative (*n*=31)	*p*-value
CRP (mg/L), mean (SD)	63.7 (59.9)	22.1 (37.7)	0.0006
WCC (× 10^9/L), mean (SD)	12.3 (4.3)	7.5 (3.0)	0.01
CK (IU/L), mean (SD)	4 948 (4 122)	935 (1 440)	<0.0001
Aldolase (mU/L), mean (SD)	38.6 (36.6)	18.7 (16.0)	0.04
AST (IU/L), mean (SD)	235 (396)	69.8 (78.9)	0.03

IIMs = idiopathic inflammatory myopathies; CRP = C-reactive protein; WCC = white cell count; CK = creatine kinase; AST = aspartate aminotransferase.

ILD is the most prevalent of these complications in our setting. Clinical symptoms such as a dry cough and dyspnoea were accurate predictors of severity and progression of disease when compared with PFT results. The presence of Velcro crackles was a predictor of UIP. Pulmonary infections, specifically PTB, were common in this study. Pulmonary symptoms may present before the onset of myositis, and there should therefore be a high index of suspicion for SARDs in these patients.

Declaration. MW is a member of the editorial board. The research for this study was done in partial fulfilment of the requirements for TH's MMed (Int Med) degree at the University of the Witwatersrand.

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Author contributions. TH, NG, MW: study conception and design. TH: data collection. TH, MT, NG, MW: analysis and interpretation of results. All authors reviewed the results and approved the final version of this manuscript.

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Conflicts of interest. None.

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