Long-term survival of patients with idiopathic inflammatory myopathies: anatomy of a single-centre cohort

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Abstract

Objective
We aimed to characterise clinical manifestations, disease course, treatment, and mortality of IIM patients. We have also attempted to identify predictors of mortality in IIM.

Methods
This was a retrospective single-centre study including IIM patients fulfilling the Bohan and Peter criteria. Patients were divided in 6 groups: adult-onset polymyositis (APM), adult-onset dermatomyositis (ADM), juvenile-onset dermatomyositis, 'overlap' myositis (OM), cancer-associated myositis, and antisynthetase syndrome. Sociodemographic, clinical and immunological features, treatment, and causes of death were recorded. Survival analysis and predictors of mortality was performed using Kaplan-Meier and Cox proportional hazards regression.

Results
A total of 158 patients were included with a mean age at diagnosis of 40.8±15.6 years. Most patients were female (77.2%) and Caucasian (63.9%). The most frequent diagnoses were ADM (35.4%), OM (20.9%) and APM (24.7%), respectively. Most patients (74.1%) were treated with a combination of steroids and one-to-three immunosuppressive drugs. Interstitial lung disease, gastrointestinal and cardiac involvement affected 38.5%, 36.5% and 23.4% of the patients, respectively. The survival rates at 5, 10, 15, 20 and 25 years of follow-up were 89%, 74%, 67%, 62% and 43%, respectively. During a median follow-up of 13.6±10.2 years, 29.1% have died, infection being the most common cause (28.3%). Older age at diagnosis (HR1.053, 95% CI 1.027-1.080), cardiac involvement (HR 2.381, 95% CI 1.237-4.584), and infections (HR 2.360, 95% CI 1.194-4.661) were independent predictors of mortality.

Conclusion
IIM is a rare disease with important systemic complications. Early diagnosis and aggressive treatment of cardiac involvement and infections could improve survival of these patients.

Key words
idiopathic inflammatory myopathies, long-term survival, autoantibodies

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Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of immune-mediated systemic diseases characterised by chronic muscle inflammation often associated with progressive proximal muscle weakness and a variety of systemic manifestations. The classification of IIM can be divided in five main groups: adult-onset polymyositis (APM), adult-onset dermatomyositis (ADM), juvenile-onset dermatomyositis (JDM), 'overlap' myositis (OM) linked to another autoimmune rheumatic disease (such as systemic lupus erythematosus or rheumatoid arthritis) and inclusion body myositis (IBM) (1). More recently, myositis-specific autoantibodies (MSA) have helped to refine the classification, and now APM are usually classified as immune-mediated necrotising myopathy (IMNM) or anti-synthetase syndrome (ASyS) (2). The OM patients are often associated with myositis-associated autoantibodies (MAA), such as anti-RNP, anti-KU, and anti-Ro-52 (2). Finally, IIM, especially ADM, can be associated with cancer (CAM) notably in males older than 45 years (3).

Although the clinical trial evidence is poor, a variety of drugs are used to reasonable effect in IIM (1). These include corticosteroids, methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine (AZA), cyclophosphamide (CCF), rituximab (RTX), tacrolimus (TAC), cyclosporin (CsA), intravenous immunoglobulin (IvIg), and there is some emerging evidence that JAK inhibitors may be helpful (1, 4, 5). Even though these drugs have helped improving survival and minimising steroid requirements, they have important adverse events such as hepatotoxicity and infection (5).

Before the generalised use of steroids and immunosuppressants, the mortality rate was as high as 50-65% (6, 7). However, in the last decades the prognosis has substantially improved, with recent studies reporting 5 and 10-year survival rates of 86% and 77%, respectively (8). Malignancy, infections, lung and cardiovascular complications are reported as the most common cause of death in IIM-patients (8-16). There is an increasing interest in studying IIM mortality, however, most studies have a relatively short follow-up period, usually less than 10 years (6, 7, 10, 14, 16).

Our aim with this study was to describe a cohort of IIM patients, followed in a single centre for a period of up to 59 years. We have reviewed the clinical manifestations, immunology, clinical course, drugs used and causes of death. We have also attempted to assess predictors of mortality in IIM.

Methods

Data source

We conducted a retrospective study of patients diagnosed with IIM followed at University College Hospital, London, between 1963 (most from 1979) and June 2022. Patients fulfilling three or four of the Bohan and Peter criteria were included (17), and those with IBM diagnosis were excluded. Patients were divided into six groups: APM, ADM, JDM, CAM, OS and ASyS. The following variables were collected following the careful review of physical and electronic clinical notes: sociodemographic (gender, age, ethnicity); duration of symptoms before diagnosis (months); presence/absence of upper/lower limb muscle weakness (UL/LL); highest creatinine kinase (CK) level; presence/absence of myopathic changes in the electromyography (EMG), muscle magnetic resonance imaging (MRI) and biopsy results; autoantibodies (antinuclear, MAS, MAA); treatment, disease course [monophasic (MM), relapsing/remitting (RR), chronic persistent (CP)]; extra muscular involvement (heart, lung, gastrointestinal, skin ulcers, calcinosis, joints, other); disease complications (cardiovascular disease, malignancy, infections); duration of follow-up (years), cause of death and age at time of death. CK levels were considered abnormal when above the upper limit (UL), according to lab reference level. Patients were divided in five groups (normal-2x UL; 2x-5x UP; 5x-10X UP; >10x UL). Antinuclear antibody (ANA) was considered positive if titres of equal to or higher than 1/80 were recorded. Cardiac involvement was defined as heart failure, myocarditis, pericarditis,

ischaemic disease, valvopathy and arrhythmias. Lung involvement was defined as interstitial lung disease (ILD) diagnosed by high resolution computed tomography (HRCT), pleurisy and pulmonary hypertension (confirmed by right heart catheterisation). Gastrointestinal (GI) involvement was defined as gastroesophageal reflux (GERD) or dysphagia. Joint involvement was defined as inflammatory arthralgia or arthritis (on physical examination or ultrasound). Only infections which required hospitalisations were recorded. Malignancy was considered as associated with myositis if has occurred 1 year before/after the IIM-diagnosis. Monophasic disease (M) was defined as having only one initial episode of active disease; remitting-relapsing disease (RR) as having multiple flares separated by disease-free periods, and chronic persistent (CP) disease as having persistence disease activity despite treatment. Duration of symptoms was defined as the number of months between the beginning of symptoms and diagnosis. Follow-up was defined as the number of years between diagnosis and the last appointment in our department or time of death. Cause of death as obtained through review of death certificates, general practitioner records and hospital notes.

Statistical analysis
Continuous data were presented as mean (standard deviation) or median (interquartile range) for variables with skewed distribution, and categorical variables as absolute number/percentage. The Kolmogorov-Smirnov test was used as test of normality.
Survival rates at 5, 10, 15, 20 and 25 years were estimated using the Kaplan-Meier analysis. The log rank test was used to assessed significant differences in survival curves between subgroups. The Cox proportional hazards regression was used to assess predictors of mortality. Variables of interest such as age at diagnosis and gender, plus variables with $p<0.20$ in the univariate analysis were included in the multivariate analysis. Thereafter, variables which lost statistical analysis were excluded from the model.

Table I. Descriptive analysis of all patients with inflammatory myositis.

	All patients n=158	Deaths n=46	Alive n=112	*p*-value
Sociodemographic characteristics				
Gender (Female)	122 (77.2)	33 (71.7)	89 (79.5)	NS
Ethnicity				
Caucasian	101 (63.9)	32 (69.6)	69 (61.6)	
African	29 (18.4)	8 (17.4)	21 (18.8)	NS
South Asian	15 (9.5)	5 (10.9)	10 (8.9)	
Asian	12 (7.6)	-	12 (10.7)	
Other	1 (0.6)	1 (2.2)	-	
Age at diagnosis (years)	40.8 ± 15.6	43.72 ± 14.4	39.7 ± 16.0	NS
Age groups (years)				
< 20	17 (10.8)	1 (2.2)	16 (14.3)	
20-39	59 (37.3)	20 (43.5)	39 (34.8)	NS
40-59	63 (39.9)	17 (37)	46 (41.1)	
> 60	19 (12)	8 (17.4)	11 (9.8)	
Disease category				
APM	39 (24.7)	16 (34.8)	23 (20.5)	
ADM	56 (35.4)	14 (30.4)	42 (37.5)	
JDM	11 (7)	-	11 (9.8)	NS
CAM	5 (3.2)	2 (4.3)	3 (2.7)	
Anti-Synthetase syndrome	13 (8.2)	1 (2.2)	12 (10.7)	
Overlap syndrome	33 (20.9)	12 (26.1)	21 (18.8)	
Delay in diagnosis (months)	7.94 ± 12.33	8.26 ± 16.93	7.79 ± 9.66	NS
Highest CK	4422 ± 7633	5458 ± 6088	3972 ± 8203	NS
Muscle involvement				
Only UL or LL/none	17 (10.8)	2 (4.3)	15 (13.4)	NS
UL and LL	141 (89.2)	44 (95.7)	97 (86.6)	
EMG (myopathic), n=128	104 (81.3)	37 (90.2)	67 (77)	NS
Muscle biopsy (myopathic), n=130	101 (77.7)	39 (90.7)	62 (71.3)	**0.014***
Muscle MRN (myopathic), n=132	54 (40.9)	10 (27.0)	44 (46.3)	**0.043***
ANA positive	98 (62.4)	24 (52.2)	74 (66.1)	NS
Anti-LA, n=141	14 (9.9)	5 (11.9)	9 (9.1)	NS
Anti-RO, n=140	33 (23.6)	9 (21.4)	24 (24.5)	NS
Anti-SM, n=140	8 (5.7)	3 (7.1)	5 (5.1)	NS
Anti-RNP, n=129	20 (15.5)	8 (22.9)	12 (12.8)	NS
Anti-synthetase, n=140	46 (32.9)	17 (40.5)	29 (29.6)	NS
Anti-Jo1, n=140	39 (27.9)	17 (40.5)	22 (22.4)	**0.029***
Anti-OJ, n=72	1 (1.5)	0 (0)	1 (1.5)	NS
Anti-PL12, n=73	4 (6.0)	0 (0)	4 (6.0)	NS
Anti-PL7, n=73	2 (3.0)	0 (0)	2 (3.0)	NS
MSA positive, n=100	62 (62.0)	18 (39.3)	44 (39.1)	NS
Anti-Mi2, n=85	8 (9.4)	1 (7.7)	7 (9.7)	NS
Anti-MDA5, n=66	1 (1.5)	0 (0)	1 (1.6)	NS
Anti-SAE, n=69	2 (2.9)	0 (0)	2 (3.2)	NS
Anti-TIF1Y, n=65	6 (9.2)	0 (0)	6 (10.0)	
Anti-NXP2, n=65	0 (0)	0 (0)	0 (0)	
Anti-SRP, n=86	4 (4.7)	1 (8.3)	3 (4.1)	
Disease course				
MP	50 (31.6)	11 (23.9)	39 (34.8)	
RR	56 (35.4)	17 (37)	39 (34.8)	NS
CP	52 (32.9)	18 (39.1)	34 (30.4)	
Extra-muscular involvement, n=156				
Cardiac	37 (23.7)	18 (40.9)	19 (17.0)	**0.002***
Lung	60 (38.5)	22 (50.0)	38 (33.9)	NS
GI	57 (36.5)	19 (42.2)	38 (34.2)	NS
Skin ulcers	15 (9.6)	4 (9.1)	11 (9.8)	NS
Joint	67 (42.9)	16 (34.4)	51 (45.5)	NS
Calcinosis	11 (7.1)	4 (9.1)	7 (6.3)	NS

ADM: adult-onset dermatomyositis; APM: adult-onset polymyositis; ASyS: anti-synthetase syndrome; CAM: cancer-associated myopathy; CK: creatine kinase; CP: chronic persistent; EMG: electromyography; GI: gastrointestinal; JDM: juvenile-onset dermatomyositis; LL: lower limb; MMF: mycophenolate mofetil; MRN: magnetic resonance; MSA: myositis-specific autoantibodies; OM: overlap myositis; MP: monophasic; RR: relapse and remitting; SD: standard deviation; UL: upper limb.
Categorical variables are presented in n (%) and continuous variables in mean (SD).

SPSS v. 25 was used for statistical analysis and significance level was defined as 2-sided p<0.05.

Results

One hundred and fifty-eight patients were recruited in this retrospective analysis (Table I). Majority were females (77.2%), and the most common ethnic origin was Caucasian (63.9%). The mean ages at diagnosis were 40.81 years (SD 15.6), 43.72 years (SD 14.4) and 39.7 years (SD 16.0), respectively. Most patients (39.9%) were aged between 40 and 59 years. The diagnoses were: ADM in 56 (35.4%), APM in 39 (24.7%), ASS in 13 (8.2%) and OS in 33 (20.9%). In cancer associated myositis (CAM, n=5) group, the most common cancer was found to be breast cancer (4) followed by peritoneal carcinoma (1). In terms of muscle involvement, most patients (89.2%) had upper and lower limb involvement (UL+/LL+) followed by five with isolated lower limbs (UL- / LL+), and two with only upper limb involvement (UL+ / LL-). Among the patients whose results were available, 98 (62%) were ANA positive, 62 (39.2%) had positive myositis specific antibodies (39 anti-Jo1, 8 Mi-2, six TIF-1 gamma, four SRP and PL12, two PL7 and with SAE, one each MDA-5, OJ and PL12). In 54.4% of patients, CK levels were higher than 10 times the upper limit of normal. EMG, muscle biopsy and MRI reports were available in 128, 130 and 132 patients, respectively. Results were compatible with an inflammatory myopathy in 65.8%, 63.9% and 34.2% of cases, respectively. The biopsy was normal in 18.4% of the patients. Among patients whose muscle biopsy results were available (n:130), after excluding OS (33) and CAM (5) patients, the compatibility of new EULAR/ACR classification criteria for adult and juvenile IIMs were assessed in total of 92 patients. Eighty-five, 4 and 3 patients were found to meet a definitve, probable and possible diagnosis. Mean delay in diagnosis was 7.94 months (SD 12.3). Among extra-muscular involvement, joint was the most common (42.4%) followed by lung (38%), GI (36.1%), and cardiac (29.7%). Of note, 15 (9.5%) patients had skin ulcers and 11 (7%) had calci-

Table II. Follow-up, treatment and cause of death.

	All patients n=158	Deaths n=46	Alive n=112	p-value
Treatment (ever)				
Azathioprine	116 (73.4)	38 (82.6)	78 (69.6)	NS
Methotrexate	77 (48.7)	19 (41.3)	58 (51.8)	NS
Cyclosporine	27 (17.1)	6 (13.0)	21 (18.8)	NS
Tacrolimus	9 (5.7)	5 (10.9)	4 (3.6)	NS
Mycophenolate mofetil	38 (24.1)	5 (10.9)	33 (29.5)	**0.013***
Cyclophosphamide	39 (24.7)	17 (37.0)	22 (19.6)	**0.027***
Rituximab	42 (26.6)	11 (23.9)	31 (27.7)	NS
IVIg	56 (35.4)	19 (41.3)	37 (33.0)	NS
Immunosuppression				
Steroid	9 (5.7)	4 (8.7)	5 (4.5)	
Steroid + 1 IS	48 (30.4)	13 (28.3)	35 (31.3)	
Steroid + 2 IS	37 (23.4)	10 (21.7)	27 (24.1)	NS
Steroid + 3 IS	32 (20.3)	10 (21.7)	22 (19.6)	
Steroid + ≥4 IS	31 (19.6)	9 (19.6)	22 (19.6)	
Follow-up duration (years), mean (SD)	13.61 ± 10.239	15.28 ± 9.98	12.92 ± 10.308	
Complications, n=156				
Cardiovascular risk factors	70 (46.1)	26 (60.5)	44 (40.4)	**0.025***
Cardiovascular events	13 (8.3)	6 (13.6)	7 (6.3)	NS
Malignancy	26 (16.7)	14 (31.8)	12 (10.7)	**0.001***
Infections	54 (34.6)	30 (68.2)	24 (21.4)	**<0.001***
Cause of death, n=46				
Infection	13 (28.3)			
Malignancy	9 (19.6)			
Cardiac	5 (10.9)			
Pulmonary hypertension	3 (6.5)	-	-	-
ILD progression	2 (4.3)			
CKD progression	1 (2.1)			
Other	2 (4.3)			
Unknown	11 (23.9)			

CKD: chronic kidney disease; CP: chronic persistent; ILD: Interstitial lung disease; IS: immunosuppression; IVIg: intravenous immunoglobulin; MP: monophasic; RR: relapse and remitting; SD: standard deviation.
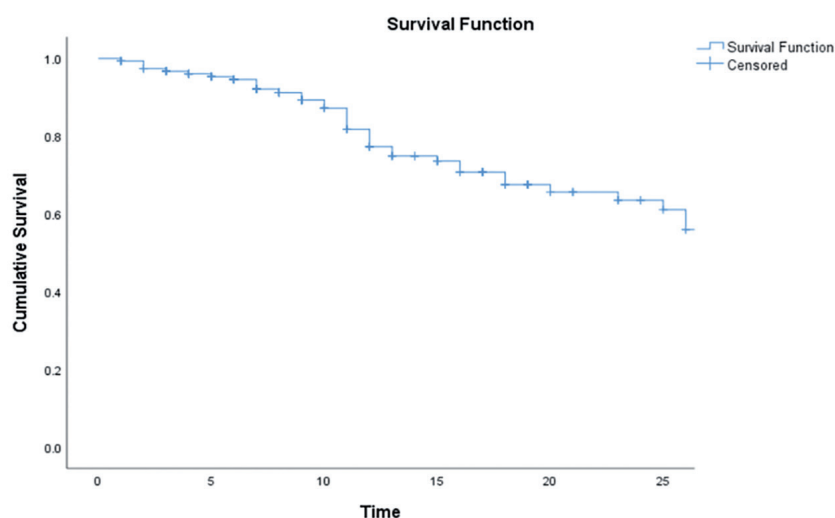

Fig. 1. Overall survival curve at distinct follow-up times (5, 10, 15, 20 and 25 years).

Years	0	5	10	15	20	25
IIM	158	134	86	56	35	26

nosis. The disease course was characterised as RR in 56 (35.4%), MP in 50 (31.6%) and CP in 52 (32.9%). Steroids were used in all patients, and more than
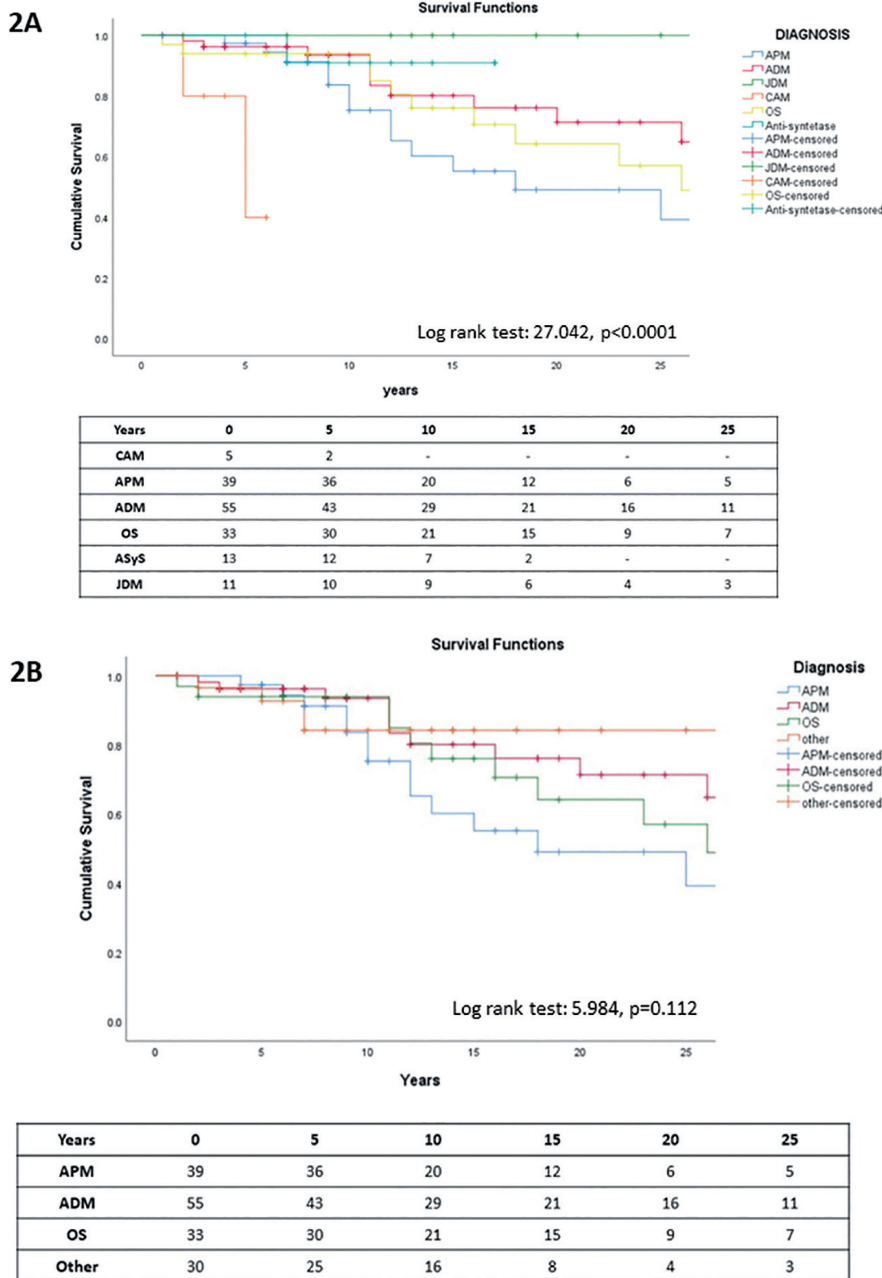
2A

Survival Functions

Log rank test: 27.042, p<0.0001

Years	0	5	10	15	20	25
CAM	5	2	-	-	-	-
APM	39	36	20	12	6	5
ADM	55	43	29	21	16	11
OS	33	30	21	15	9	7
ASyS	13	12	7	2	-	-
JDM	11	10	9	6	4	3

2B

Survival Functions

Log rank test: 5.984, p=0.112

Years	0	5	10	15	20	25
APM	39	36	20	12	6	5
ADM	55	43	29	21	16	11
OS	33	30	21	15	9	7
Other	30	25	16	8	4	3

Fig. 2. Survival curves according to the diagnosis.
A: crude analysis with all the diagnosis; **B**: after regrouping patients to increase statistical power.
ADM: adult-onset dermatomyositis; APM: adult-onset polymyositis; ASyS: anti-synthetase syndrome; CAM: Cancer-associated myopathy; JDM: Juvenile-onset dermatomyositis; OM: overlap myositis[a].

ninety percent also received one or more immunosuppressive drugs, with the most preferred agents of azathioprine (AZA), methotrexate (MTX), IVIG, mycophenolate (MMF), cyclophosphamide (CYC), rituximab (RTX), and cyclosporine (CyC). Among all medications, those who received MMF at any time had a lower mortality rate (10.9 vs. 29.5, p=0.013). In contrast, mortality was higher among patients ever given CYC (37 vs. 19.6, p=0.027). (Table II).

The mean duration of follow-up was 13.6 years (SD 10.2 years), with a minimum of 1 year and a maximum of 59 years of follow-up. Notwithstanding, there was a great proportion of patients with more than 15 years of follow-up (35.4%) and 22.1% had more than 20 years of follow-up.

The survival rates at 5, 10, 15, 20 and 25 years of follow-up were 89%, 74%, 67%, 62% and 43%, respectively (Fig. 1). During this period of follow-

up, 46 (29.1%) died, most commonly due to infection (28.3%), followed by malignancy (19.6%), cardiovascular events (10.9%), pulmonary hypertension (6.5%), ILD progression (4.3%), chronic kidney disease progression (2.1%), other (4.3%) and unknown causes (23.9%) (Table II). Cardiac events were found to be heart failure (13), conduction and/or rhythm abnormalitis (13), pulmonary hypertension (10), pericardial disease (pericarditis and/or effusion) (10), myocardial ischemia (8), valvulopathies (4), myocarditis (3), and stroke (2). The mortality rate was 34.3% in ADM patients, 30.4% in APM, 20.9% in OS, and 8.2% in ASyS. In a non-adjusted survival analysis, CAM showed higher mortality rates, followed by APM, OS, ADM, ASyS and JDM (Fig. 2A). Yet, after regrouping patients given the low number of patients and shorter follow-up time with some of the diagnosis, such as CAM, JDM and ASyS, there were no differences in mortality rates (Fig. 2B). Death occurred after a mean 15.2 (SD 10.0) years of follow-up. Most patients were female and Caucasian (71.7% and 69.6%, respectively), with a mean age at death of 59.9 years (SD 15.8). Sixteen (34.8%) had ADM, 14 (30.4%) had APM and 12 (26.1%) had OS. In this group, ANA and MSA were positive in 24 (52.2%) and 18 (39.3%). In the subgroup analysis of ASyS patients who were dead (n= 17), all were those known to be positive for the anti-Jo-1 antibody (p=0.029). Mortality rates according to disease courses were seen as 39.1% in CP, followed by 37% in RR and 23.9% in MP.

In univariate analysis, older age at diagnosis (HR 1.043, 95% CI 1.020-1.066), CAM (HR 8.052, 95% CI 1.525–42.510), Jo1 (HR 1.877, 95% CI 1.011–3.484), MSA (HR 2.645 95% CI 0.899–7.856), cardiac involvement (HR 2.131, 95% CI 1.164–3.901), severe infections (HR 2.150, 95% CI 1.127–4.102) and malignancy (HR 2.021 95% CI 1.063–3.841) were associated with a higher risk of death. We found no association between gender, ethnicity, disease course, CK level, ANA, treatment, delay in diagnosis, lung, GI and joint involvement, skin ulcers and calcinosis,

and mortality. In a multivariate analysis using a Cox regression model, including age at diagnosis, gender, cardiac involvement, infections and malignancy, older age at diagnosis (HR1.053, 95% CI 1.027–1.080), cardiac involvement (HR 2.381, 95% CI 1.237–4.584), and infections (HR 2.360, 95% CI 1.194–4.661) were independent predictors of mortality (Table III).

Discussion

The present study reports a description of clinical characteristics, mortality and prognostic factors in a large cohort of well characterised and carefully followed up patients with IIM in the United Kingdom.

In our cohort, there was a female predominance, as expected, with a slightly higher female-to-male ratio of 3.4 than previous studies (2.0-2.9) (10, 11). The most common ethnic group was Caucasian, and the mean age at diagnosis was similar with the literature (10, 11). In our study, we have observed ADM (35.4%) as the most frequent diagnosis, followed by APM (24.7%), OM (20.9%), and ASyS (8.2%), which is relatively different in contrast to previous data (10, 11). However, recent advances in the availability of more myositis specific antibodies have improved our understanding in helping to optimise the classification of myositis subgroups better than before. This might explain the decrease in APM patients in our study population. In addition, when we determined whether our patients met the latest EULAR/ACR classification criteria for adult and juvenile IIMs in our study population, 92.3% (85/92) of patients had a definitive diagnosis. Organ involvement also differ considerably between cohorts. In our study, cardiac, lung and GI involvement affected 23.7%, 38.5% and 36.5% of the patients, respectively while Slovenian and Italian cohorts reported much lower cardiac involvement (11.5% and 14.3%), and Spanish REMICAM cohort reported lower ILD prevalence (27%) (8, 12, 15). A Japanese cohort reported almost a doble ILD prevalence (64%) and lower cardiac and GI involvement (17% and 21%, respectively) (14). These differences may

be explained by different proportions of types of IIM, such as ASyS, differences in organ involvement definitions; underdiagnosis due to the retrospective study designs, but also real geographic and ethnic differences. As reported by Danieli *et al.*, about 1/3 of patients each exhibited a MM, RR and CP disease course (12). As expected, most patients were treated with a combination of steroids and immunosuppressive drugs, with azathioprine being the most common (73.4%). There were some differences in drug preferences between studies, with other authors favouring the use of methotrexate (12, 15), which may be due to drug policies, but also differences in organ involvement. In our study, we found that mortality rate was lower in patients who were ever given MMF, whereas those who received cyclophosphamide at anytime had higher mortality rates. This observation should not be over interpreted because patients who received those medications generally had different clinical profiles. Thus, we have tended to 'reserve' CYC for those patients with life-threatening organ involvement. Of note, no differ-

ence in mortality was found for other medications.

To the best of our knowledge, we describe the IIM cohort with the longest mean follow-up time of almost 15 years, with more than one fifth of our cohort having 20 years or more of follow-up. Previously, most other studies have a span time of 10 years or lower (8, 12, 15, 16). Additionally, we reported higher 5 and 10-year survival rates (89% and 74%, respectively) than older studies (6, 7, 16, 18), but similar to recent cohorts (8, 10, 12, 14), which may reflect better management and treatment strategies.

In our cohort, about 1/3 of the patients died after an average of 15 years of follow-up. In a literature review (19), cancer, lung, cardiac complications, and infections were the main causes of death in IIM patients. In our cohort, infection was the most common cause of death (28.3%), followed by malignancy (19.6%), similar to the Spanish cohort (8). However, ILD complications are one of the most common cause of death in some cohorts, while in our study it only represented (4.3%) (12,

Table III. Predictors of mortality in idiopathic inflammatory myopathies.

| Variables# | Univariate analysis | | Multivariate analysis | | |
| | HR (95% CI) | HR | 95% CI | | p-value |
			Lower	Upper	
Gender (female)	1.267 (0.666-2.412)	1.296	0.638	2.631	0.473
Age at diagnosis (years)	**1.043 (1.020-1.066)***	1.053	1.027	1.080	**<0.0001***
Ethnicity (Caucasian)	-	#	#	#	#
Afro-Caribbean	0.875 (0.399-1919)				
Other	0.660 (0.275-1.583)				
Diagnosis (APM)	-	#	#	#	#
ADM	0.519 (0.252-1.066)				
JDM	-				
CAM	**8.052 (1.525-42.510)***				
OS	0.611 (0.288-1.298)				
ASyS	0.290 (0.038-2.217)				
EMG	1.996 (0.710-5.609)	#	#	#	#
Muscle biopsy	2.744 (0.973-7.442)	#	#	#	#
JO1	**1.877 (1.011-3.484)***	#	#	#	#
MSA	2.645 (0.891-7.856)	#	#	#	#
MMF	0.418 (0.164-1.061)	#	#	#	#
Cardiac involvement	**2.131 (1.164-3.901)***	2.381	1.237	4.584	**0.009***
Lung involvement	1.401 (0.773-2.541)	#	#	#	#
Joint involvement	0.561 (0.302-1.041)	#	#	#	#
Infections	**2.180 (1.127-4.102)***	2.360	1.194	4.661	**0.013***
Malignancy	**2.021 (1.063-3.841)***	1.923	0.972	3.805	0.060

ADM: adult-onset dermatomyositis; APM: adult-onset polymyositis; ASyS: anti-synthetase syndrome; CAM: cancer-associated myopathy, EMG: electromyography; JDM: juvenile-onset dermatomyositis; MMF: mycophenolate mofetil; MSA: myositis-specific autoantibodies; OM: overlap myositis.
*p<0.05; #Variables with p<0.20 in the univariate analysis were included in the multivariate analysis and further excluded when losing statistical significance.

14). Some factors may explain these differences, such as methodological differences, with some authors considering pulmonary infections as an ILD complication, as well as differences in ILD severity, with Asian patients having a more severe pulmonary disease. Several factors have being described as carrying a worse prognosis, such as infections, malignancy, older age, male gender, dysphagia, cardiac involvement and ILD (8, 10, 12, 16). In our cohort, the major predictors of death were older age, cardiac involvement and infections. Interestingly, neither ILD or malignancy emerged as significant mortality risk in the multivariate analysis, both frequently reported as worse prognosis factors. One possible explanation could be the fact we included infections in the Cox regression model, which was the main cause of death in our cohort, and it is well established that cancer and ILD are risk factors for severe infections. However, ILD showed no association with death neither in either the univariate nor in the multivariate analysis. Retrospective cohort studies in two European Nordic countries, did not find an association between ILD and mortality as well (15, 20). In contrast, Yamasaki *et al.* reported ILD to be the main cause of death in IIM patients (14). This may reflect different genetic background, with ILD severity varying between countries and ethnicity. As expected, in the univariate analysis, CAM was associated with higher mortality, mainly due to the associated malignancy. We did not find any association between gender, ethnicity, skin ulcers, dysphagia and mortality, as previously reported in other cohorts (19).

The present study has some limitations. Its retrospective, monocentric and observational design may lead to missing data. Second, it includes patients diagnosed many years ago, which not only limited the ability to obtain information from the hospital paper records, but also leads to some heterogeneity in the cohort characteristics. The easy availability of MRI scanning has only been possible in the past 15 years, approximately. The only MSA available for a decade was anti-Jo1. Therefore, some

of the most recently identified MSA could not be tested in the older patients (although stored sera did help us somewhat), and, in some cases, MSA were only performed many years after the diagnosis and treatment, which might have caused false negative results. Additionally, in some of the patients EMG, MRN and muscle biopsy were only performed after starting the treatment, potentially leading to false negative results. These points have led to a suboptimal analysis of the contribution of autoantibodies, EMG, biopsy and MRN to IIM prognosis. Finally, patients exhibited varying lengths of follow-up, with some of the older patients being lost to follow-up, leading to survival bias.

In contrast, this study has several strengths. It is one of the largest cohorts of IIM in Europe and has the longest mean follow-up time in the literature, as far as we are aware, contributing to an increasing knowledge about clinical characteristics along with survival and mortality rates in IIM patients. These findings emphasise the need for close follow-up of these patients, malignancy screening and early treatment of severe organ involvement, such cardiac, but also aggressive and early treatment of infections.

Conclusion

IIM is a rare disease with important systemic complications. Older age at diagnosis, cardiac involvement, and infections are independent predictors on mortality. Early diagnosis and aggressive treatment of cardiac involvement and infections could improve survival of these patients.

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