Infections as a predominant cause of death in adult patients with idiopathic inflammatory myopathies

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Abstract

Objective

To evaluate causes of death in the single-centre Polish cohort of patients with idiopathic inflammatory myopathies (IIM) and to identify risk factors associated with fatal outcomes.

Methods

Electronic medical database was retrospectively analysed, data on the clinical symptoms, serological profiles, administered treatment and outcomes in IIM patients were collected. Two subgroups were distinguished - the deceased and the survived group. Statistical analysis was performed to identify differences between the subgroups and risk factors contributing to fatal outcomes.

Results

79 patients with IIM were identified, most frequently with antisynthetase syndrome, dermatomyositis and polymyositis. Among them 9 patients (11.39%) deceased. The mean age at the time of diagnosis was 57.10 ± 14,59years old. Median diagnostic delay reached 5 months. The majority of the deaths (77.78%) occurred within the first 18 months after IIM diagnosis. As compared to the survivors, patients with fatal outcomes were more frequently affected by cardiac involvement (p=0.026), suffered from concomitant autoimmune disorders (p=0.028) were treated with mycophenolate mofetil (p=0.005) and cyclophosphamide (p=0.006). 89.89% of all deaths in our cohort were caused by various infections, predominantly of the respiratory tract. Although 10.13% of the patients had a history of malignancy, none of the deaths was caused by malignancy.

Conclusion

Patients with IIM associated with cardiac involvement and concomitant autoimmune diseases may be at higher risk of fatal outcomes. Infections were the predominant cause of death in our cohort of patients. The majority of fatal outcomes occurred at the relatively early stage of the disease.

Key words

idiopathic inflammatory myopathy, myositis, mortality, infection, risk factor

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Introduction

Idiopathic inflammatory myopathies (IIM) are a group of connective tissue diseases with one of the highest mortality rates out of all rheumatic disorders. Several subtypes have been identified including dermatomyositis (DM), cancer associated dermatomyositis (CADM), polymyositis (PM), antisynthetase syndrome (ASS), immune-mediated necrotising myopathy (IMNM) and inclusion body myositis (IBM); each of them is characterised by distinct pathogenesis and unique clinical presentation (1, 2). Following the identification of myositis-specific (MSA) and myositis-associated antibodies (MAA) serologically based subtypes began to be distinguished, contributing to even higher heterogeneity of the disease (3). According to the literature, 10-year mortality in IIM ranges from 28.6% to 60.1% (4). So far, versatile risk factors of fatal outcomes have been identified. However, available data remain not fully consistent, indicating high heterogeneity of IIM and the possible impact of ethical and geographical discrepancies. Limited data is available for the central European cohorts. The aim of our study was to evaluate causes of death in the single-centre Polish cohort of patients with IIM, as well as to identify risk factors associated with fatal outcomes.

Materials and methods

The study covered a period of 75 months, from March 2017 to June 2023. The cohort of patients with a clinically-based diagnosis of myositis, hospitalised at the Department of Rheumatology and the unified outpatient rheumatology clinic of the University Clinical Hospital-Central Veterans' Hospital (USK-WAM) in Lodz, Poland, was established by the Authors. Electronic medical records of the identified patients were retrospectively analysed. Compliance with the EULAR/ACR classification criteria from 2017 was verified by the Authors based on the clinical data and results of additional tests available in the medical records. From the initially established cohort, 7 patients were excluded due to uncertain diagnoses or incomplete data. Fig. 1 summarises the flow-chart methodology of the study group formation. From the electronic medical documentation selected data was retrieved, including demographic details, data on the course of the disease and clinical symptoms, results of serological tests (myositis-specific-MSA and myositis-accompanying antibodies-MAA, assessed by immunoblot), administered treatment, concomitant disorders and disease outcome. Subgroups of the survivors and the deceased patients were distinguished and compared in order to identify discrepancies. The risk analysis was conducted, odd ratios for the fatal outcome were identified. Data was analysed statistically with the STATISTICA 13 software, with the use of the Shapiro-Wilk test, χ^2 test, Mann-Whitney U-test, and odds ratio.

The study was a retrospective analysis based on the digital database; no procedures were performed on the subjects. Therefore, no consent from the bioethical committee was required.

Results

Characteristics of the study group

The study group consisted of 79 patients with a confirmed diagnosis of IIM, based on the EULAR/ACR classification criteria from 2017. Female to male ratio was 40:39 (50.63%: 49.37%). The mean age at the time of diagnosis was 57.10±14.59 years old. The mean BMI was 27.16±5.38, median 25.95. Mean disease duration was 42.04 months in overall cohort (ranging from 0 to 317 months), including mean of 24.44 months in the deceased group and 44.30 months in the survived patients. The most frequently diagnosed subtype of IIM was ASS in 32.91% (n=26) of the patients, followed by DM in 30.38% (n=24) and PM in 12.65% (n=10). In 7.59% (n=6) of the cohort CADM was diagnosed, while 10.12% (n=8) of the patients suffered from IMNM. For the analysis, CADM was defined as malignancy occurring within three years of the diagnosis of inflammatory myopathy, including both the period prior to and after the onset of myositis. The most commonly identified MSA were antisynthetase antibodies in 39.24% (with

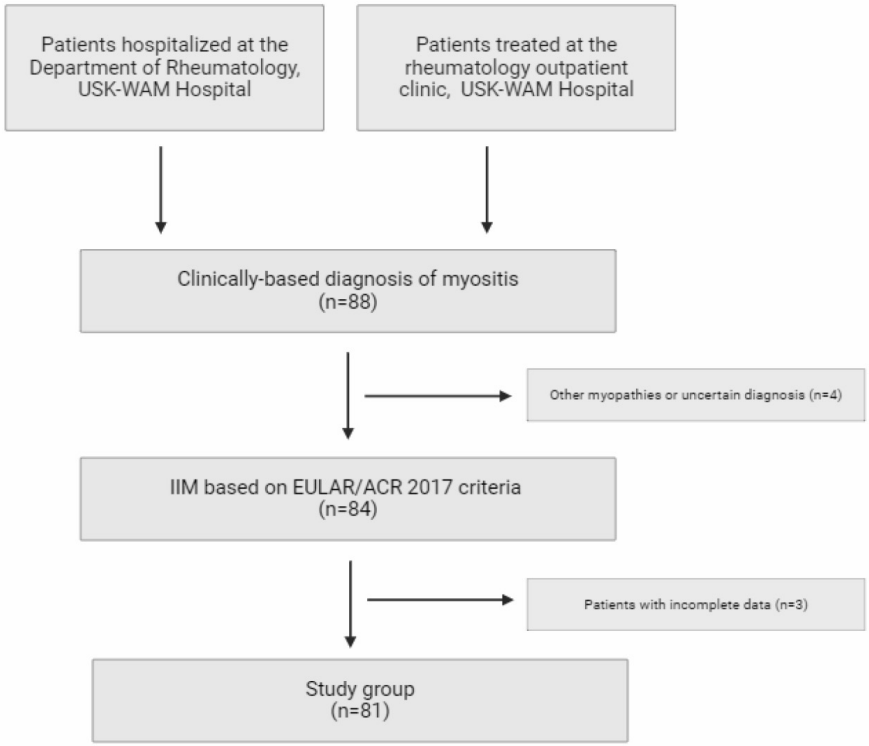


Fig. 1. Methodology of the study group formation.
USK-WAM: Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz, Central Veteran Hospital; n: number of patients.

anti-Jo-1 and anti-PL-7 being the most prevalent), anti-Mi2 in 18.99% and anti-SRP in 22.78%. The most prevalent MAA were anti-Ro52, identified in almost 1 in 3 patients. Detailed data on the serological profiles is presented in Figures 2A and 2B. Diagnostic delay, defined as the time from the first IIM symptoms to the final diagnosis of IIM, ranged from 0 to 204 months, with a median of 6 months and a mean value of 22.85±38.88 months. In 29 patients (36.71%) diagnostic delay was at least 12 months. During the observation period, 9 patients (11.39%) died. Table I compares the subgroups of the survived and deceased patients. No statistically significant differences were observed for the demographical data, structure of IIM subtypes and serological profiles (Table I).

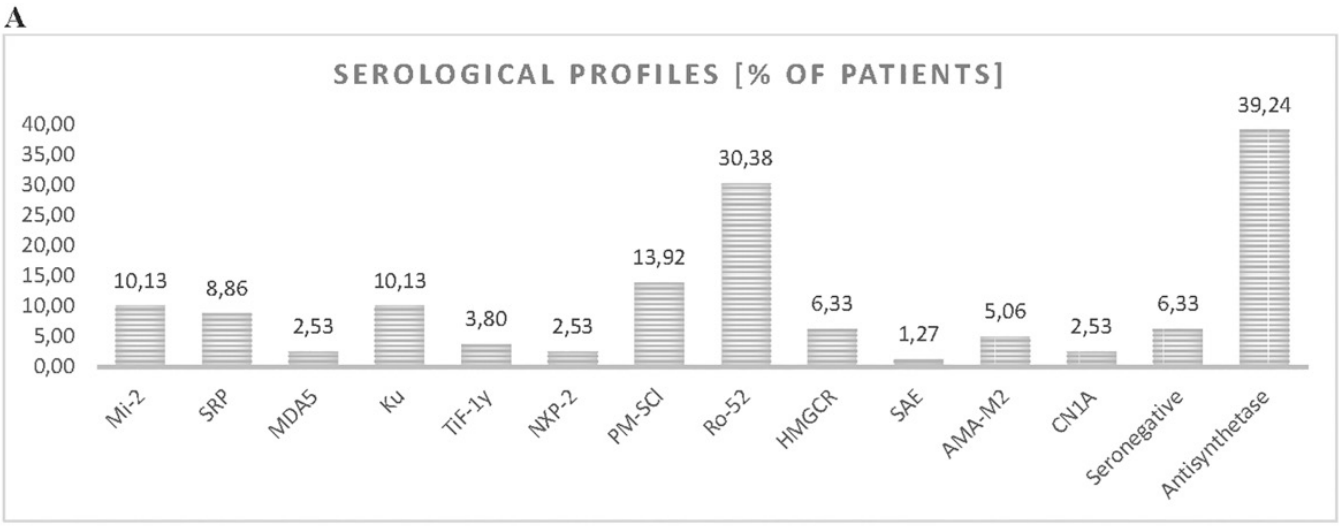
Clinical symptoms and comorbidities

The most common clinical presentation was muscle involvement, observed in 93.67% of the patients. Arthralgia affected 56.96% of the population, however, arthritis was confirmed only in 15.19%. Interstitial lung disease with an incidence of 46.83% remained one of the most prevalent clinical manifestations. Pathognomonic cutaneous lesions, such as heliotrope rash and Gottron's papules/sign were identified in respectively 21.52% and 27.85% of the cohort, while other erythematosus lesions (V sign, shawl sign, holster sign and erythema in other localisations) were present in 40.50%. Cutaneous ulcerations were relatively rarely observed, only in 5.06% of the cohort. Features typically associated with ASS, such as mechanic's hands, Raynaud's phenomenon and fever occurred in respectively 17.72%, 15.19% and 13.92%. Cardiac involvement was confirmed by additional tests in 17.72% of the patients, including diagnosis based on cardiac MRI in 3 patients and echocardiography or Holter ECG examination in 9 individuals. Dysphagia was declared by 8 patients (10.13%). Table II presents the incidence of the clinical symptoms in both of the study groups. As compared to the survivors, patients with fatal outcomes were more frequently affected by cardiac involvement (44.44% *vs*. 14.29%, p=0.026). No statistically significant differences were observed for the prevalence of the remaining clinical symptoms.

The most common concomitant diseases were hypertension in 54.43% of the patients, hypothyroidism in 31.64%, hyperlipidaemia in 26.58% and gastritis/peptic ulcer disease/gastroesophageal reflux disease in 24.05%. Impaired bone density, defined as osteoporosis or osteopenia, was diagnosed in 22.78%. A high prevalence of cardiovascular diseases was noted, including arrhythmias in 15.19%, heart failure in 18.99%, ischaemic heart disease in 6.17% and the past medical history of thromboembolic incidences in 7.59%. 12.66% of patients suffered from type 2 diabetes. Chronic respiratory diseases were relatively rarely diagnosed, including asthma in 8.86% and chronic obstructive pulmonary disease in 2.53% of the studied population. Table II compares the incidence of comorbidities in the survived and deceased groups. A higher prevalence of concomitant autoimmune diseases was observed in the deceased subgroup as compared to the survivors (33.33% *vs*. 8.57%, p=0.0277 and included entities such as autoimmune hepatitis, diabetes mellitus type 1, rheumatoid arthritis, autoimmune labyrinthitis and Sjogren disease. Autoimmune thyroid diseases were not included due to inconsistent reporting of data-some patients reported thyroid dysfunction, but without specification of the aetiology. Although hypertension, heart failure, arrhythmias, hypothyroidism, chronic obstructive pulmonary disease and chronic renal disease were also more frequent in patients with fatal outcomes, the differences did not reach statistical significance.

Treatment

Almost all of the patients received glucocorticosteroids (GCS) at any stage of the disease (96.20%). 36 patients (45.57%) were treated with intravenous pulses of methylprednisolone at any stage of the disease. Comparing survivors and deceased patients no statistically significant differences were noted as for the type of GCS used or way of GCS administration (intravenous or oral intake). Azathioprine and



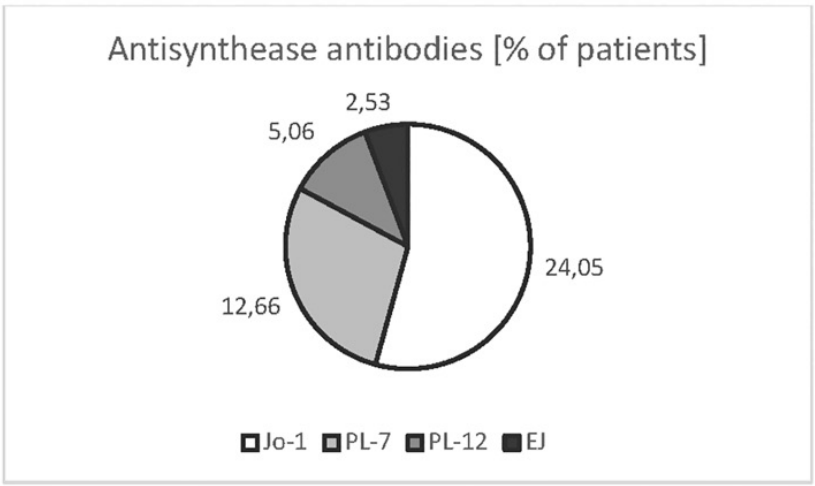


Fig. 2. Antibodies detected in the study participants.
A: presents the prevalence of each detected myositis-specific and myositis-associated antibodies.
B: presents the spectrum of antisynthetase antibodies detected in the study group.

methotrexate were frequently added to GCS and administered respectively in 65.82% and 26.58% of the patients. 16 patients (20.25%) received intravenous immunoglobulins. Table III compares therapeutic options administered in the deceased and surviving groups. Patients with fatal outcomes were more frequently treated with mycophenolate mofetil and cyclophosphamide as compared to the survivors, respectively 55.56% *vs*. 15.71%, p=0.005 and 33.33% *vs*. 5.71%, p=0.006.

Fatal outcomes

During the follow-up period, 9 patients died (11.39% of the study group). The vast majority of deaths (89.89% of all deaths) were caused by various infections. In 6 patients fatal outcome was triggered by respiratory tract infections, which in half of the affected patients (n=3) led to exacerbation of interstitial lung disease. In 1 patient neuroinfection caused by Herpes simplex occurred and in another one patient abscess in the gluteal area was complicated by sepsis. Only in some of the patients, aetiological factors were identified, including *cytomegalovirus (CMV)* reactivation (n=1), *E.coli* and *C.albicans* identified in the respiratory tract (n=1) and sepsis caused by *S.heamolyticus* and *K.pneumoniae ESBL+* (n=1). Only one death was of a non-infectious cause-a sudden cardiac arrest in a patient with progressive fibrosis of the cardiac conduction system in the course of IIM. The mean time from the first IIM symptoms to the fatal outcome was 46±40.90 months with a median of 24 months, however, considerable discrepancies were observed between individual patients, ranging from 6 months to 128 months. The majority of the deaths (77.78%) occurred within the first 18 months after IIM diagnosis. Detailed data on the deceased patients is presented in Table IV.

In 8 patients malignancy was diagnosed. The most frequent types were planoepitheliale lung cancer in 2 patients and renal clear cell carcinoma in other 2 patients. The remaining subtypes included: malignant melanoma, ovarian lymphoma, testicular cancer and pancreatic intraductal papillary mucinous neoplasm. Noteworthy, none of the patients with neoplastic disease died during observation period.

To identify factors associated with an increased risk of fatal outcomes in IIM risk analysis was performed. Cardiac involvement (OR 4.80, p=0.0376), treatment with mycophenolate mofetil (OR 6.70, p=0.011), cyclophospha-

Table I. Demographical data, subtypes of IIM and serological profiles in patients with IIM. No statistically significant differences were observed between deceased and survived patients.

Feature	Deceased (n=9)	Survivors (n=70)	*p*
Gender F:M	66.67%:33.33% (n=6:3)	49%:51% (n=34:36)	0.307
Age at the time of diagnosis [years]	59.4 ± 16.9	56.8 ± 14.4	0.477
Disease duration [months]	24.44	44.30	0.282
BMI	29.39 ± 6.65	26.87 ± 5.18	0.189
Diagnostic delay			
Median [months]	7.00	5.00	0.891
Average [months]	23.3 ± 39.2	22.8 ± 39.1	
Min-max [months]	0-120	0-204	
Diagnostic delay ≥5 months	55.56% (n=5)	55.22% (n=37)	0.985
Diagnostic delay ≥ 1 year	44.44% (n=4)	37.31.% (n=25)	0.679
Diagnostic delay > 2 years	22.22% (n=2)	23.88.% (n=6)	0.957
Subtype of IIM			
DM	0.% (n=0)	34.29.% (n=24)	X
ASS	55.56% (n=5)	31.43.% (n=22)	0.434
PM	11.11% (n=1)	12.86.% (n=9)	0.882
IMNM	22.22% (n=2)	8.57.% (n=6)	0.201
CADM	0% (n=0)	8.57.% (n=6)	X
Serological profile			
Anti-Jo-1	22.22% (n=2)	28.57% (n=20)	0.689
Anti-PL-7	22.22% (n=2)	15.71% (n=11)	0.620
Ant-PL-12	0% (n=0)	11.43% (n=8)	X
Anti-EJ	0% (n=0)	2.86.% (n=2)	X
Anti-OJ	0% (n=0)	1.43.% (n=1)	X
Any antisynthetase	44.44% (n=4)	38.57.% (n=27)	0.734
Anti-Mi-2	22.22% (n=2)	18.57% (n=13)	0.793
Anti-SRP	22.22% (n=2)	22.86% (n=16)	0.966
Anti-MDA-5	0% (n=0)	7.14.% (n=5)	X
Anti-Ku	0% (n=0)	17.14.% (n=12)	X
Anti-TIF-1y	11.11% (n=1)	7.14.% (n=5)	0.672
Anti-NXP-2	0% (n=0)	7.14.% (n=5)	X
Anti-Pm-Scl	0% (n=0)	22.86.% (n=16)	X
Anti-Ro52	44.44% (n=4)	32.86.% (n=23)	0.490
Anti-SAE	0% (n=0)	8.70% (n=6)	X
Anti-HMGCR	0% (n=0)	7.15.% (n=5)	X
Anti-AMA-M2	11.11% (n=1)	5.80% (n=4)	0.540
Anti-Cn1A	0% (n=0)	2.86% (n=2)	X
Seronegative	11.11% (n=1)	5.71.% (n=4)	0.531

X: statistical analysis not applicable.

mide (OR 8.25, p=0.015) and concomitant autoimmune disorders (OR 5.33, p=0.043) were confirmed to increase the risk of death.

Discussion

IIM is a highly heterogeneous group of connective tissue diseases. In recent years attention has been attracted to various clinical courses and outcomes of autoimmune diseases depending on the geographic and ethical discrepancies. Little data is available for IIM patients from the central European region. To the best of our knowledge, we presented one of the largest characterised and described cohorts from Poland. Similarly to the study by Rams *et al*., Wisłowska *et al*. and Masiak *et al*. we noted a high incidence of antisynthetase antibodies in our cohort. The clinical phenotypes observed in our cohort seem to correspond with other Polish studies (5-7).

Mortality in IIM patients is significantly higher than in the general population (8, 9). The risk of death seems to be the highest at the beginning of the disease. In the Swedish cohort, mortality was outstandingly high within the first year of IIM diagnosis, yet remained constantly elevated even 10 years after the disease onset (10). Similarly, in the Mexican DM population, poorer survival was observed within the first 4 years of the disease (11). This remains in line with our study, in which the majority of patients deceased within the first 18 months after IIM diagnosis. However, in some of the patients, we noted considerable diagnostic delay, resulting in a falsely short period from IIM diagnosis to a fatal outcome. Since many of the studies did not provide diagnostic delay, we cannot exclude the possibility of similar bias in the literature.

Many studies aimed to evaluate potential risk factors for death in IIM. So far, numerous factors associated with poor outcome were identified including clinical features such as older age, male gender, presence of cancer, skin ulcerations, heart involvement, arthritis, ILD and pulmonary involvement, concomitant severe infections, dysphagia, fever (in ASS), chronic progressive or relapsing course, treatment delay, therapy with rituximab, methotrexate (in DM) and azathioprine (in DM) as well as laboratory results such as hyperferritinaemia, baseline elevation of acute phase reactants, increased serum aspartate aminotransferase and neutrophil-to-lymphocyte ratio (NLR), lymphocytosis (in ASS), severe lymphopenia (in anti-MDA5+DM), presence of anti-Ro-52 antibodies (in ASS), low platelets count (in DM), raised erythrocyte sedimentation rate (in DM), abnormalities in serum creatine kinase levels (in DM), positive SS-A (in PM), increased levels of IgA at the diagnosis, minimal value of creatine phosphokinase (9, 11-28). It remains partially in line with our study, as we noted higher mortality in patients with cardiac involvement. Furthermore, we found that concomitant autoimmune disorders and treatment with mycophenolate mofetil could be associated with a higher risk of fatal outcomes, which to our knowledge was not previously noted. Since mycophenolate mofetil was administered mostly in patients with ILD, further studies are needed to evaluate if a higher risk of death should be truly attributed to the therapy itself or is rather the consequence of a more severe course of the disease in the deceased patients. Unfortunately, in many patients exact data on the severity of ILD was not available and short observation period limits the credibility of progression evaluation.

Table II. Prevalence of clinical symptoms and comorbidities in the study group with comparison between deceased and survived patients.

Feature	Deceased (n=9)	Survivors (n=72)	*p*
Clinical symptoms			
Muscle involvement (weakness and/or myalgia)	100% (n=9)	92.86.% (n=67)	0.4074
Arthralgia	66.67% (n=6)	55.71% (n=39)	0.532
Arthritis	22.22% (n=2)	14.29.% (n=10)	0.532
Heliotrope rash	0% (n=0)	24.29.% (n=17)	X
Gottron's papules/sign	33.33% (n=3)	27.14.% (n=19)	0.696
Mechanic's hands	33.33% (n=3)	15.71% (n=11)	0.1926
Other skin erythematosus lesions	44.44% (n=4)	40.00.% (n=28)	0.798
Raynaud's phenomenon	11.11% (n=1)	15.71.% (n=11)	0.717
Cutaneous ulcerations	11.11% (n=1)	4.29% (n=3)	0.379
Interstitial lung disease	55.56% (n=5)	45.71.% (n=32)	0.577
Cardiac involvement	**44.44% (n=4)**	**14.29% (n=10)**	**0.026**
Dysphagia	11.11% (n=1)	10.00.% (n=7)	0.917
Fever	0% (n=0)	15.71.% (n=11)	X
Comorbidities			
Malignancy (current or in past medical history)	0% (n=0)	11.43.% (n=8)	X
Heart failure	33.33% (n=3)	17.14.% (n=12)	0.244
Ischemic heart disease	11.11% (n=1)	5.56% (n=4)	0.514
Arrhythmias	33.33% (n=3)	18.06% (n=13)	0.278
Diabetes type 2	11.11% (n=1)	12.86.% (n=9)	0.882
Hyperlipidaemia	0% (n=0)	30.00.% (n=21)	X
Hypothyroidism	33.33% (n=3)	31.43.% (n=22)	0.908
Gastritis/peptic ulcer disease/ gastroesophageal reflux	0% (n=0)	27.14.% (n=19)	X
Asthma	0% (n=0)	10.00.% (n=7)	X
Chronic obstructive pulmonary disease	11.11% (n=1)	1.43% (n=1)	0.082
Osteoporosis/osteopenia	11.11% (n=1)	23.65% (n=17)	0.375
Thromboembolic incidents	11.11% (n=1)	6.99.% (n=5)	0.672
Chronic renal disease	22.22% (n=2)	5.71.% (n=4)	0.078
Concomitant autoimmune diseases	**33.33% (n=3)**	**8.58% (n=6)**	**0.028**

X: statistical analysis not applicable.

Table III. Therapeutic options used in IIM cohort with comparison between deceased and surviving patients.

Treatment	Deceased (n=9)	Survivors (n=70)	*p*
Glucocorticosteroids	100% (n=9)	95.83% (n=69)	0.533
Prednisone p.o.	88.89 (8)	71.64 (48)	0.270
Methylprednisolone p.o.	44.44 (4)	67.16 (45)	0.181
Dexamethasone p.o.	11.11 (1)	4.48 (3)	0.403
Methylprednisolone pulses i.v.	44.44% (4)	45.71 (32)	0.943
Methotrexate	0% (n=0)	30.00.% (n=21)	X
Azathioprine	66.67.% (n=6)	65.71.% (n=46)	0.955
Calcineurin inhibitors	0.% (n=0)	5.71% (n=4)	X.
Cyclophosphamide	**33.33.% (n=3)**	**5.71% (n=4)**	**0.006**
IVIG	22.22% (n=2)	20.00.% (n=14)	0.876
Mycophenolate mofetil	**55.56% (n=5)**	**15.71.% (n=11)**	**0.005**
(Hydoxy)chloroquine	0% (n=0)	8.57% (n=6)	X
Leflunomide	0% (n=0)	5.71% (n=4)	X
Nintedanib	0% (n=0)	1.43% (n=1)	X
Adalimumab	0% (n=0)	1.43% (n=1)	X
Rituximab	11.11% (n=1)	2.78% (n=2)	0.212
Glucocorticosteroids + any immunosuppressive agent	77.78% (7)	84.29% (59)	0.620
At least 2 immunosuppressive agents	44.44% (4)	42.86% (30)	0.928

X: statistical analysis not applicable.

Interestingly, apart from other autoimmune conditions, concomitant diseases did not seem to impact the prognosis. On the contrary, according to the literature oedema of the hands, female gender, elevated serum albumin levels and longer disease duration were found to be associated with better prognosis (14, 26). In a single Chinese cohort contrary results were found, as male gender decreased the risk of death (29). Moreover, lower mortality was observed in patients treated with IVIG as compared to patients on chronic glucocorticosteroids or immunosuppressants (17). Since in Poland IVIG is a second-line therapy, available for patients with treatment-resistant IIM, we reported a relatively small proportion of patients on IVIG therapy.

According to the literature, mortality seems to differ depending on the clinical and serological profiles of the patients, however, data on the risk of death in various IIM subtypes remain inconsistent. The worst prognosis was reported for patients with cancer-associated myositis, clinically amyopathic DM and overlap myositis (17, 22, 30). DM, CAM and OM were associated with poorer prognosis as compared to PM (16, 22, 26). Patients with antisynthetase phenotype were characterised by a lower risk of death (31), however not in the juvenile population (32). Similarly, in the cohort from Oman, patients with juvenile DM were characterised by the highest mortality rate out of all IIM types (33). In our study, we did not observed differences in the risk of death according to IIM subtype, yet it need to be highlighted that juvenile patients were excluded from our study. In the Chinese cohort, the anti-MDA-5-positive patients had the highest mortality rate as compared to patients with other MSA. Rapidly progressive ILD was found to be the strongest predictor of mortality in those patients, while malignancy was an independent risk factor for the patients with antisynthetase antibodies, anti-TIF1γ antibodies and seronegative patients (34). Surprisingly, in our cohort none of the deceased patients was anti-MDA5 positive. However, in our cohort there were only 2 patients with anti-MDA5 positive myopathy, which remains in line with data from the literature, indicating lower prevalence of MDA5 positivity in Caucasian population (35). Moreover, in both of our patients the disease duration was

Table IV. Detailed data on the deceased patients.

n	Gender	Age at diagnosis (years)	Diagnostic delay (months)	IIM subtype	Clinical symptoms	Antibodies against	Treatment; *-directly before death	Cause of death	Time from diagnosis to death (months)
1	M	76	120	IMNM	Muscle weakness / pain, cardiac involvement	SRP	GCS*, AZA infection	respiratory	8
2	F	67	48	DM	Muscle weakness / pain, Gottron's sign/papules, cardiac involvement	Mi-2, Ro-52	GCS*, AZA	sudden cardiac arrest	16
3	F	64	16	ASS	Muscle weakness/ pain, arthralgia, Gottron's sign/papules, other erythematosus lesions, ILD,	PL-7, Ro-52	GCS*, MMF*, AZA, CYC	infectious exacerbation of ILD	67
4	F	70	12	ASS	Muscle weakness/ pain, arthralgia, ILD	Mi-2b, TIF1, CENB, Th/To, NOR90	GCS*	infectious exacerbation of ILD	17
5	M	80	7	ASS + SSc	Muscle weakness/pain, arthralgia, arthritis, mechanic's hands, Raynaud's phenomenon, skin ulcerations, cardiac involvement, ILD, dysphagia	PL-7, Scl70	GCS*, MMF*	respiratory infection	1
6	M	39	3	ASS	Muscle weakness/pain, arthralgia, arthritis, mechanic's hands, other erythematosus lesions, cardiac involvement, ILD	Jo-1, Ro-52, AMA-M2	GCS*, AZA*, MMF, IVIG, CYC	neuroinfection	71
7	F	31	3	IMNM	Muscle weakness/pain, arthralgia, other erythematosus lesions	SRP	GCS*, MMF*, AZA, IVIG, RTX, plasmapheresis	respiratory infection	16
8	F	61	1	PM	Muscle weakness/pain	seronegative	GCS*, AZA	sepsis from abscess in the gluteal area	5
9	F	47	0	ASS	Muscle weakness/pain, arthralgia, Gottron's sign/papules, mechanic's hands, other erythematosus lesions, ILD	Jo-1, Ro-52, SS-A, NOR90, RP155	GCS*, AZA, MMF, CYC	infectious exacerbation of ILD	6

rather short (3 months and 19 months). Bhansing *et al*. observed that patients with SSc-PM overlap have a worse survival rate compared with patients with SSc (30). Our results do not confirm these previous observations, as we did not observe any differences in mortality depending on the subtype of IIM or serological status. However, it should be noted that our cohort was small and diverse, which may hinder stating statistically significant conclusions. Ethical and socioeconomic factors may also contribute to the mortality *e.g*. in African patients high early mortality was found (7.8–45%) and deceased patients tended to be younger than in other continents (36). In our cohort all the patients were of Caucasian origin.

Various infections were the leading causes of death in our cohort, responsible for almost 90% of fatal outcomes. This remains in line with the data available in the literature, as infections, malignancies, diseases of the cardiovascular and respiratory systems were identified among the most common causes of death in IIM patients (10-12, 19, 25, 37-43). Depending on the cohort, distinct cause prevailed *e.g*. Campar *et al*. and Limaye *et al*. showed that cardiovascular damage was the main cause and a major contributor to death (44, 45), malignancy contributed to the majority of fatal outcomes in Slovenia (23), while in cohorts from New Zealand, China, USA, India, Oman and in the MyoCite cohort infections were the most common cause of death (4, 33, 37). Although in 8 of our patients malignancies were diagnosed, none of the patients died directly due to neoplasm. This may indicate high physicians' awareness of the well-known co-occurrence of cancer and IIM. Furthermore, in our unit malignancy screening and regular monitoring are routinely practised in patients with IIM. However, it should be noted that the observation period in some of the patients was relatively short. Long-term follow-up is needed to provide more accurate data on the real prognosis in this subgroup of patients.

It is noteworthy that, since 2001 growing trends have been observed in the proportion of infection-associated IIM mortalities (42). Infections, especially opportunistic, emerge as an underrecognised problem of the highest clinical importance in IIM patients. Increased risk of serious infections seems to be independent of patients' age, as it was demonstrated both in juvenile and adult DM populations. Infections in IIM patients may occur in different sites. In the American study, DM was significantly associated with infections of the skin, musculoskeletal system, respiratory tract, brain, heart, gastrointestinal system as well as generalised infections (46). One of the most frequent infections in IIM is aspiration pneumonia, which is a potentially life-threatening condition (47). This remains in line with the studies on the Australian cohort, in which among the 26 patients with infection as the primary cause of death, 19 had pneumonia, five had septic shock, one had a lung abscess and one had sepsis (45). Similarly in our

cohort, respiratory tract infections or exacerbations of ILD due to respiratory infections prevailed. In the study by Adhoubi *et al*., sepsis was responsible for 50% of deaths in IIM population (33). However, in our cohort only 1 of the deceased patients died due to generalised infection.

Infections, predominantly bacterial pneumonia, bacteraemia and opportunistic fungal infections, were identified as the strongest predictors of hospital mortality in the large cohort of USA patients with DM and PM (48). The analysis of the USA cohort revealed that infections were the cause of hospitalisation in 13% and the leading cause of in-hospital mortality (34% of all deaths) (49). Noteworthy, infectious complications, with the predominance of pneumonia, remained one of the major causes of admissions to the intensive care unit. In 63.2% of the patients, infections were triggered by opportunistic agents, mostly *Aspergillus sp*. and *P. jiroverci*. In the vast majority of the patients admitted to the intensive care unit progressive interstitial lung disease and acute respiratory failure led to IIM exacerbation and organ failure. Unfortunately, in almost 80% of the IIM patients hospitalisation in the intensive care unit resulted in fatal outcomes (50). Several factors for mortality in the intensive care unit were identified in the Chinese cohort, including DM subtype, lymphocytopenia, Pa02/Fi02 ratio, APACHE II score and the presence of acute respiratory failure (50).

The spectrum of potentially harmful opportunistic pathogens for IIM patients was evaluated in several cohorts. Surprisingly high incidence was noted for viral infection triggered by varicella zoster virus (VZV) and cytomegalovirus (CMV), which affected 44.4% of the population. CMV reactivation was frequent, especially in patients treated with calcineurin inhibitors and cyclophosphamide. Lymphopenia (<900/μL) at the onset of DM was found to be significantly associated with the risk of CMV reactivation (51). Therefore, it seems reasonable to consider prophylaxis in patients with lymphopenia, before administration of calcineurin inhibitors or cyclophosphamide. Cases of fatal viral hepatitis were documented (42). In 16.7% of the patients fungal (*Candida albicans, Pneumocystis jirovecii*) and parasitic (*Toxoplasma gondii, Leishmania spp*) infections occurred. Out of bacterial infections, *Klebsiella pneumoniae* and *Acinetobacter baumannii* were the most commonly identified pathogens, and co-infection with the two pathogens was frequently diagnosed (42). In our cohort, deceased patients had CMV reactivation, *E.coli* and *C.albicans* identified in the respiratory tract and sepsis caused by *S.heamolyticus* and *K.pneumoniae ESBL+*.

According to the literature, more than half of all opportunistic infections occurred within the first year of diagnosis. Moreover, patients with fever at the IIM onset, Cushing's syndrome, disabilities and concomitant cancer were found to be at higher risk of opportunistic infections (46, 52). Ethical and socioeconomic discrepancies may contribute to the observed associations (46). Long-lasting and high-dose glucocorticosteroid therapy, biological drugs or subsequent administration of at least 4 immunosuppressive agents seem to increase the risk of opportunistic infections (52). In our cohort, the majority of the infections with fatal outcomes occurred during the first 18 months after IIM diagnosis, confirming previous observations of the highest risk at the onset of the disease.

Screening and prophylaxis of chronic and opportunistic infections are of a high priority in managing patients with rheumatic diseases, which was reflected by the EULAR recommendations (53). Although the recommendations pertain to autoimmune inflammatory rheumatic diseases in general, as no dedicated guidelines for IIM are available, strategies could be applied also to IIM. Based on the recommendations, screening for latent tuberculosis, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) is recommended prior to immunosuppressive treatment. The status of VZV-immunity should be established and non-immune patients should be offered post-exposure prophylaxis. It is advised to consider *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis in patients with autoimmune inflammatory rheumatic diseases receiving high doses of glucocorticoids, especially in combination with immunosuppressants (53). As IIM patients are usually treated with intense immunosuppression PCP prophylaxis seems to be justified also in this group of patient. While planning infection prophylaxis in IIM, geographical discrepancies should be considered. In endemic regions, *e.g*. in India, tuberculosis was found to be one of the leading aetiological factors, easy to underdiagnose as it frequently manifests with extra-pulmonary symptoms (54, 55). In Poland, latent screening for tuberculosis, HBV, HCV and HIV is mandatory when registering a patient for a treatment programme with bDMARDs or csDMARDs and is considered reasonable in patients on immunosuppressive therapy.

The importance of vaccinations was emphasised in the EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases, which included among others patients with IIM (56). Influenza and pneumococcal vaccinations are strongly advised for the majority of patients and HAV, HBV, VZV vaccinations for high-risk patients. Recommendations highlight that the risk of VZV infection is exceptionally high in IIM patients. Patients with autoimmune inflammatory rheumatic diseases should receive tetanus toxoid vaccination and human papillomavirus vaccination as recommended in the general population except for patients on B cell therapy, who could benefit more from passive immunisation with tetanus immunoglobulins. In Poland, there are no specific national recommendations regarding vaccinations in patients on immunosuppressive agents, therefore European recommendations should be followed. The importance of infections in mortality and the above recommendations are unfortunately not fully reflected in the reimbursement of vaccines, *e.g*. in Poland VZV and pneumococcal vaccinations are partially reimbursed yet only in immunosuppressive patients older than 65 years old. Our observations demonstrated that fatal outcomes

are not restricted to senile patients. Extending reimbursement indications also to younger patients would be advisable.

Conclusions

Infections were found to be the predominant cause of death in our cohort of patients. The majority of fatal outcomes occurred at the relatively early stage of the disease. The initial period of treatment, requiring intensive immunosuppression, may pose a significant risk of potentially life-threatening complications and should therefore be considered a period of special vigilance. More attention should be attracted to latent infection screening, infection prevention and rational immunosuppression in patients with IIM. Moreover, patients with cardiac involvement and concomitant autoimmune diseases may be at higher risk of fatal outcomes and therefore require increased vigilance.

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