

Clinical epidemiology of the Idiopathic Inflammatory Myopathies

A population-based study from South-east Norway

Thesis for the degree of Doctors of Philosophy (Ph.D.)
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Lists of papers:

Paper 1: Prevalence and clinical characteristics of adult polymyositis and dermatomyositis; -data from a large and unselected Norwegian cohort

Cecilie Dobloug , Torhild Garen , Helle Bitter , Johan Stjärne , Guri Stenseth , Lars Grøvle , Marthe Sem , Jan Tore Gran, Øyvind Molberg. Ann Rheum Dis. 2014 Apr 2. doi: 10.1136/annrheumdis-2013-205127. [Epub ahead of print]

Paper 2: High prevalence of Inclusion Body Myositis in Norway; a population based clinical epidemiology study.

Cecilie Dobloug , Ellen Ann Antal , Line Sveberg , Torhild Garen , Helle Bitter , Johan Stjärne, Lars Grøvle , Jan Tore Gran Øyvind Molberg. Eur J Neurol. 2014 Dec 21. doi: 10.1111/ene.12627. [Epub ahead of print]

Paper 3: Survival and cancer risk across unselected, Norwegian idiopathic inflammatory myopathy cohorts.

Cecilie Dobloug , Torhild Garen , Cathrine Brunborg, Jan Tore Gran Øyvind Molberg
Submitted.

1.1 Introduction.

1.1.0 The concept of IIM

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of chronic, systemic disorders; defined by progressive loss of striated muscle tissue and with an unknown aetiology[1]. These disorders are on the basis of unique clinical, histopathological, immunological and demographic features differentiated into three distinct and major subsets; polymyositis (PM), dermatomyositis (DM) and sporadic inclusion body myositis (sIBM).[2, 3]. This introduction will first describe PM/DM separately and then make a separate part for sIBM

1.1.1 History of PM/DM

Approximately 125 years ago, Unverricht recorded the first description in the medical literature of PM. This was followed a year later by Jacoby's article in the United States literature. The earliest well documented cases were by Eaton in 1954, followed by an article by Walton in 1956, then two by Barwick and Walton in 1960 and 1963. In the 70s Rose and Walton and finally Pearson published clinical patterns of PM/DM.[3-7] What gradually emerged from these studies was a clear clinical picture of PM and DM. In the recent years new information about pathology and serum auto-antibodies has increased the knowledge and awareness of these systemic autoimmune disorders.

1.1.2 Clinical features of PM and DM:

DM and PM are characterized clinically by progressive symmetrical proximal muscle weakness of the shoulders, neck and hips.[2] The muscle involvement can have an acute, sub-acute or a more insidious onset, but the patients typically begin to notice fatigue of their

muscles or weakness when climbing stairs, walking, rising from a sitting position, combing their hair, or reaching for items in cabinets that are above their shoulders. Muscle tenderness (myalgia) and stiffness may occur.[2, 8] The typical rash of DM patients include; Heliotrope rash, Gottron's papules or sign, V and Shawls sign. The rashes are purple-to-erythematous, scaly, and may demonstrate both hyperpigmentation and hypopigmentation, as well as telangiectasia and epidermal atrophy in sun-exposed areas-typically described as V-sign at the front of chest and Shawl seen on the neck after sun-exposure (poikilodermatous).[9, 10] Heliotrope rash typically affects the eyelids and are described as purple and edematous, while the Gottron's papules are typically described as erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. This manifestation may occur over the finger joints, elbows, knees, malleoli and toes. The Gottrons sign is erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable.

There are however some DM patients with rash, which have little or no muscle disease. These subgroups of DM are called amyopathic or hypomyopathic DM or Clinically Amyopathic Dermatomyositis (CADM). In addition to the manifestations of skin and muscle a significant number of patients exhibit oesophageal dysmotility and dysphagia, affection of joints with the symptoms of arthralgia and arthritis, Raynaud, Sicca phenomenon, fever and flu-like symptoms and to a lesser extent calcinosis cutis and mechanic's hands.[1] Mechanic's hands are scaly, fissured hyperkeratotic lesions on the lateral and palmar surfaces hands. These fissure-like cracks in the palms of the hands are in some cases black and resemble the hands of a hard-working manual labourer, hence the name. This feature is typically seen in patients with anti-synthetase syndrome (ASS) (see later).

Both PM and DM are regarded as systemic diseases with frequent manifestations in the gastrointestinal tract, joints, pulmonary and cardiovascular systems [1, 9, 11]. Both the muscle

and skin affection may lead to severe disability and morbidity, but the major clinical problem is acute and chronic lung involvement and secondary pulmonary hypertension (PH). The prevalence of pulmonary involvement and ILD has been reported to vary between 20% and 80% in ethnically diverse populations and is considered to be a common cause of morbidity in these patients.[12-20]. Cardiac complications include heart failure, arrhythmias, ventricular dysfunction[21]. Oesophageal involvement is considered to be frequent in PM/DM occurring in 20 to 84% of patients and encompasses asymptomatic patients to life-threatening complications (aspiration pneumonia, need for total enteral feeding due to aphagia) [22, 23].

1.1.3 Classification of PM/DM

In 1975, Bohan and Peter published a classic article that suggested a set of criteria to aid in the diagnosis and classification of DM and PM [24-26]. The Peter & Bohan diagnostic criteria from 1975 are still regarded as “the gold standard” when classifying PM and DM cases for research purposes (Table 1).[27] The classical Peter and Bohan criteria include key clinical features (muscle weakness and DM rash) and laboratory parameters (serum level of muscle enzymes, electromyography (EMG) and muscle histology), but not Myositis Associated Autoantibodies (MAA) or magnetic resonance imaging (MRI) of muscle tissue (Table 1).

Revised classification criteria, building on the Peter & Bohan criteria, with inclusion of MAA and MRI were proposed by Targoff et al in 1997 (Table 2).[28]

Several investigators have proposed alternative PM/DM classification criteria (Medsger 1970, De Vere 1975, Dalakas 1991 and 2003, Tanimoto 1995, Mastalgia 2002, Hoogendijk 2004 and Christopher-Stine 2010.[2, 29-35]. Most criteria have been found to have some limitations.

The earliest criteria lack clear instructions how to rule out other forms of myopathy, and sIBM not included as a separate entity. In addition, the earliest criteria do not specify and characterize the rash in DM. The sensitivity and specificity for many confounding

dermatological and neuromuscular disorders have in addition not been evaluated. [36, 37] The limitations of the more recent criteria are that they are based on case-series from single centre, based on clinical observations, rather than data-analysis. And none have been tested for sensitivity and specificity by appropriate powered studies against all the appropriate disease confounders.[36, 37]

Table 1 Peter and Bohan Criteria

1	progressive proximal symmetrical weakness
2	Elevated serum enzymes, not only CK, but also aldolase, AST, ALT and LD.
3	Abnormal electromyogram with myopathic motor unit potentials, fibrillations, sharp waves, increased insertional irritability an abnormal electromyogram
4	Muscle biopsy evidence of necrosis of myofibers, phagocytosis, regeneration with basophils, large vesicular sarcolemma nuclei, and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size and an inflammatory exudate, often perivascular.
5	Typical skin rash of DM; including Heliotrope rash, Gottrons papules or sign.

- 3 positive criteria are classified as probable IIM
- 4 positive criteria are classified as definite IIM
- Additional positive typical skin rash of DM (No 5), classifies the patient as DM.

Table 2 Targoff diagnostic criteria for PM/DM. Any three items equals probable PM/DM and any four criteria equals definite diagnosis.[28]

Items in Targoff	
Symmetric proximal muscle weakness	1
Elevated serum enzymes, not only Creatine Kinase (CK), but also aldolase, AST, ALT and LD.	2
Abnormal electromyogram with myopathic motor unit potentials, fibrillations, sharp waves, increased insertional irritability	3
Muscle biopsy evidence of necrosis of myofibers, phagocytosis, regeneration with basophils, large vesicular sarcolemma nuclei, and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size and an inflammatory exudate, often perivascular.	4
Typical skin rash of DM; including Heliotrope rash, Gottrons papules or sign.	5
Any one of the Myositis Associated autoantibody*	6
Pathological MRI findings consistent with inflammation	May substitute criterion 1 or 2

- Including Anti-synthetase (anti-Jo 1, anti-PL 12, anti-PL 7) and anti-Mi2 and anti-SRP autoantibodies.

More recently, larger scale consensus efforts have been undertaken by the International Myositis Classification Criteria Project (IMCCP) with objectives to develop and validate new classification criteria for IIM. The methods utilized by IMCCP are the usage of candidate variables selected from published criteria. These have been assessed on international multicentre recruited IIM patients, 973 in total. Two probability score models have been

developed; Model 1: clinical variables on muscle, skin and laboratory measures. Model 2 which additionally comprised muscle biopsy variables. These two models were found superior to existing criteria, and external validating is in progress.[37]

Interestingly, preliminary data from IMCCP, presented at the EULAR-meeting in 2014 indicated that the Targoff criteria show the best sensitivity and specificity of established criteria. [37].

1.1.4 Pathology of PM/DM

Biopsies from weakened muscles in PM or DM typically show myositis with inflammatory cell infiltration of muscle tissue accompanied by degeneration and regeneration of muscle fibres. Accumulated evidence from immune-histochemical studies suggests wide heterogeneity of the infiltrates. In patients with clinical DM one often identifies peri-vascular accumulations of CD4+ T cells, B cells and plasmacytoid dendritic cells. In contrast, the infiltrates in PM and, to some degree, also in sIBM mainly consists of activated CD8+ T cells. [38]

1.1.5 Aetiology and pathogenesis of PM/DM:

By definition, the causes of PM/DM remain unknown: However, data from similar autoimmune disease support the hypothesis that these conditions result from chronic immune activation after exposure to environmental risk factors in individuals with a predisposing background.[39] Genetic associations are more linked to clinical phenotypes and autoantibodies than with myositis patients as a whole. Genetic factors for myositis also vary by age of onset, ethnicity, and environmental exposure group.[40] The genetic risk factors include polymorphism of many genes that regulate responses to environmental agents, particularly human leukocyte antigen (HLA), and cytokine and immunoglobulin genes.[41-

43]. Current findings suggest that human leukocyte antigen (HLA) genes on chromosome 6, particularly HLA DRB1*0301 and the linked allele DQA1*0501, have the strongest associations with all clinical forms of IIM in white patients.[44] Familial autoimmunity in pedigrees of idiopathic inflammatory myopathy patients suggests common genetic risk factors for many autoimmune diseases.[45]

It is speculated that the autoantigens need certain 'micro-environments for example, lung, skin, muscle or tumour tissue. And that these micro-environments need specific triggers such as UV light, infection or misdirected anti-tumour response which in turn lead to the over-expression of proteins (Jo-1, Mi-2, TIF1 and others) by apoptotic cells. It is believed that granzyme B generated fragments become immunogenic, and that corresponding autoantigens develop chemo-attractant properties leading to tissue injury and autoimmune responses. [46]

1.1.6 Myositis Specific Autoantibodies and clinical phenotypes:

Autoantibodies are common in PM and DM, and more than ten different, mutually exclusive myositis specific antibodies (MSA) have been described.[46] Interestingly, the MSA are associated with distinct clinical syndromes that often cross the classical distinction between PM and DM.[40, 47, 48] The most common of these autantibody-associated IIM syndromes are described below.

Anti-synthetase syndrome: The main MSA are the Anti-synthetase autoantibodies (ASS) which forms the largest subgroup in IIM patients. Anti Jo-1 is the most frequent one and one of the first described (Table 3). [49, 50] The ASS are mutually exclusive. ASS has been well described, and classic clinical features include myositis, interstitial lung disease (ILD), Raynaud's, mechanic's hands, Gottron's lesions, non-erosive inflammatory arthritis and fever. ILD is a major manifestation and the most commonly encountered radiological and histological patterns are Non-Specific Interstitial Pneumonia (NSIP) and Cryptogenic

Organizing Pneumonia (COP). This group of patients may have Usual Interstitial Pneumonia (UIP), the radiological and histological pattern synonymous with Idiopathic Pulmonary Fibrosis (IPF). ILD is reported in 50–95 % of ASS patients, but it is clear that even within the ASS spectrum, anti-Jo1 differs from non-anti-Jo1 ASS patients.[51-58] The non-anti-Jo1 ASS clinical phenotype may be present with lung disease first, and patients may never develop myositis, have subclinical myopathy or milder muscle disease.

Table.3. Types of Antisynthetase syndrome autoantibodies

Name	Antigen
Anti-Jo 1	Histidyl-tRNA synthetase
Anti-PL12	Alanyl tRNA synthetase
Anti-PL7	Threonyl tRNA synthetase
Anti-OJ	Isoleucyl tRNA synthetase
Anti-EJ	Glycyl tRNA synthetase
Anti-KS	Asparaginyl tRNA synthetase
Anti-Zo	Fenylalanin tRNA synthetase
Anti-Ha	Tyrosyl tRNA synthetase

Necrotizing Myopathy Syndromes; Autoimmune necrotizing myopathy (ANM) is a relatively newly recognized subgroup of IIM that are defined by common clinical and histopathological features (Table 4) [46]. Patients present with sub-acute proximal weakness with high CK levels. On muscle biopsy, characteristic features include myofibre necrosis, minimal endomysial and perivascular inflammatory infiltrate, and in some cases focal endomysial fibrosis [59]. Despite little or no muscle inflammation, ANM usually responds to immune modulatory therapy highlighting that this is an immune-mediated phenotype associated with

two specific autoantibodies (Table 4). *Other MSA* :Recently new MSA have been discovered; anti-Transcription intermediary factor -1g (anti-TIF-1g), anti-nuclear matrix protein 2 (anti-NXP2), anti-melanoma differentiating antigen 5 (anti-MDA5), anti-small ubiquitin-like modifier enzyme heterodimer 1/2 (anti-SAE1/2) and anti- cytosolic 5-nucleotidase 1A (anti-Mup44).(Table 4).

Table 4 Other Myositis Associated Autoantibodies (MSA)

	Clinical features	Reference
Anti-SRP	AMN with high CK, serious myopathy, dysphagia, cardiac muscle involvement and arthritis.	[51, 60]
Anti-HMG-coA	AMN associated with prior statin exposure, significant weakness and high CK levels.	[61, 62]
Anti-MDA5 .	Amyopathic dermatomyositis (ADM), severe, acute ILD.	[63, 64]
Anti-Mi2	Classical DM, low frequency of cancer-associated myositis (CAM),	[65]
Anti-TIF-1g	DM and Cancer associated myositis (CAM) in adults. systemic features and severe skin disease.	[66, 67]
Anti-NXP2	JDM, lower frequency adult patients	[68-70]
Anti-SAE	CADM with classic skin disease first. Later go onto develop myositis with a higher frequency of systemic involvement; dysphagia and gastrointestinal disease.	[71, 72]
Anti-MUP44	Associated with sIBM	[73, 74]

1.1.7 Epidemiology PM/DM:

The epidemiology of PM/DM is largely unknown and only a few epidemiological studies have been published. Research into these disorders has been limited by the rarity of the disease, a somewhat insidious onset, difficulties with classification and diagnostic methods, a heterogeneous study population and selection bias [75, 76]. In general, DM seems the most common and PM the least common. DM affects both children and adults, whereas PM generally occurs after the second decade of life. As to gender, when considering the DM–PM as a whole, the female/male ratio is about 2:1. The reported incidence ranges between two and eight new cases per million of inhabitants per year [39, 47, 76-78] Few studies have been undertaken in Europe. Annual incidence of 7.6 cases/million was estimated in a country-cased Swedish study[79].

Prevalence data for PM and DM vary from 5/100 000 between 21.5/100 000 depending on methods used for obtaining data, highest estimations done by calculated by medical administrative data in USA and Canada. [39, 80-82] To our knowledge, there is only one population based study on DM, with 29 cases defined solely by clinical features,[83]) and some few retrospective studies based on chart reviewing.[4, 31, 76, 79, 84-88] The largest of these chart review studies, performed in the Allegheny County in Pennsylvania from 1963-82, used predefined clinical criteria for case assignment and identified 177 PM/DM cases.

Interestingly, the study reported that the PM/DM incidence tripled during the study period.

[76]

1.1.8. Morbidity in PM/DM

Although PM and DM are regarded as treatable disorders, prognosis is not well known, as in the literature long-term outcome and prognostic factors vary widely- favourable outcome is reported to be between 18 to 90% depending on study.[27, 32, 47, 89, 90] To date, although overall prognosis appears to be better, PM and DM are still considered to be associated with increased morbidity, primarily related to severe muscle weakness and visceral involvement.[91] Recent series underline that only 20% to 40% of treated patients will achieve PM/DM remission, whereas 60% to 80% will experience a polycyclic or chronic, continuous course of the disease. PM/DM further continues to have a great impact on life in medium- and long-term follow-up, as up to 80% of treated patients are still disabled (using Health Assessment Questionnaire scores).[89, 91] Predictive factors for a poor prognosis in PM/DM patients are older age, delay in cortisone treatment, involvement of lung and cardiac systems, difficulty swallowing, cancer, and serum myositis-associated antibodies (anti-Ro52 and anti-Jo1 antibodies, anti-SRP, Anti-TIF-1g and anti-MDA5 antibodies).[12, 89, 91] Series by Marie et al. underlies the high frequency of ILD in PM/DM patients, resulting in increased morbidity and mortality rates. It also indicates that PM/DM patients should routinely be screened for ILD. Because of the poor outcome of ILD, it may require more aggressive therapy.[15]

1.1.9 Survival in PM/DM

Studies from the 1970s indicated increased mortality in PM/DM. [4, 92-95] Later work have confirmed this, but shown large variation in mortality rates, probably due to differences in patient selection, classification and loss to follow-up. [91] Peter and Bohan criteria have been applied in eight studies on mortality (table 5), [89, 90, 96-101] but only one of these eight studies was performed on an unselected population based cohort. [98] This study, which is the largest mortality study to date, performed hospital discharge searches for PM/DM cases by the 7th International Classification of Disease version 7 (ICD-7) codes and subsequent case assignment by chart review to identify 248 PM/DM patients diagnosed in Finland from 1969-1985, followed until death or 1995. Mortality rates in this study were assessed by life-tables [98], and not by matched population controls [89]. Available data indicate that major causes of death in PM/DM are cancer, infections and cardiopulmonary complications. [91, 98] Prognostic factors vary between studies, but older age, cardiopulmonary disease, cancer and the presence of MAA have all been associated with poor outcome.

Table 5 Mortality studies in patients with PM/DM

Study	Year and location	Patients with PM/DM,	Survival at 5 y,%	Mortality, %	Comments and criteria
Medsgers et al.[93]	1971 US	124	65	36.4%	1947-1968, ICDA codes and chart review. Multicentre Life-table
Benbassat et al. [102]	1985 Israel	92	52	32.6	1956-1976, chart review, Peter and Bohan (P&B) Multi-centre.
Hochberg et al. [103]	1983 US	1986 deaths attributed to PM/DM codes	n.d	Calculated Relative risk for patients according to gender, age and race.	1968 -1978. ICD-8 codes, no chart review. Nation-wide Death records from US
Marie et al. [90]	2001 France	77	77	22.1	1983-1998, chart review, no codes, (P&B), single centre.
Sultan et al. [96]	2002 UK	46	95	13	1978-1999, chart review, P&B criteria. single centre
Danko et al. [99]	2004 Hungary	162	92	12.3	1976-1997, chart review, P&B. Single centre
Airio et al. [98]	2006 Finland	248	75 (PM) 63 (DM)	60.1	1969-1985, ICD-7 code, chart review. P & B. Nation-wide
Bronner et al. [89]	2006 Netherlands	165	n.d	21	1977-1998, chart review, P&B. Multicentre.
Torres et al. [101]	2006, Spain	107	80	27.5	25 year follow-up, chart review, P&B. Single centre.
Yamasaki et al. [100]	2011, Japan	197	75	26.9	1984-2009. P&B, Sondheim's for AMD. Single centre
Yu et al. [104]	2011. China	192	76	28.6	1999-2008, chart review. Single centre
Schiopu et al. [97]	2012, US	160	77	16.9	1997-2003, ICD-9 codes, chart review. P & B. Single centre

1.1.10 Cancer risk DM/PM

The first report suggesting an association between malignancy and DM was published in 1916.[105] Since then, a large number of case series and case reports were described in the literature. However, the first case-control study confirming the association of DM/PM with malignancy was published years later in 1985.[106] Subsequent population-based retrospective cohort studies have consistently confirmed an increased risk of malignancy in the setting of DM and PM and recently in sIBM. Overall, these studies observed a 2-to 4 fold increased cancer risk in PM/DM, with highest incidence rates in the DM subset and in males older than 50 years.[105, 107-112] (Table 6), Cancer diagnosis can precede, parallel, or follow DM/PM diagnosis. The largest cancer study in PM/DM to date was a pooled analysis of data from Sweden, Denmark, and Finland.[105, 111, 112] The study included 618 DM and 914 PM patients identified by ICD-7 or ICD-8 hospital discharge diagnoses, but less than 1/3 of these cases had their PM/DM diagnosis verified by chart review [109]. Standardized Incidence Rates (SIR) were estimated using National cancer registry data as reference and found to be 3.0 in DM and modestly increased, at 1.3 in PM.[109]. A recent retrospective study on biopsy-proven IIM cases from Victoria, Australia reported increased cancer risk across all IIM subsets, including sIBM. [111] Cancer subtype analyses indicated that the most common PM/DM associated malignancies were of ovarian, lung, gastrointestinal, breast or haematological origin.[105, 109-112]

Table 6 Overview over main cancer-studies in IIM:

Study, year and location	No patients	Cancer	Case Finding	Comments
Hill [113], 2001 Sweden, Finland and Denmark	618 DM 914 PM	SIR* DM 3.0. PM	ICD-7/8 hospital discharge diagnoses, coupled to life table cancer registry	< 1/3 chart reviewed and classified by P&B
Sigurgeirsson, [112], 1992 Sweden	788 PM/DM	Relative risk DM 2.4, PM 1.8	ICD-7/8 hospital discharge diagnoses. Coupled to life table cancer registry	1/10 chart reviewed and classified by P&B
Chow [114], 1995 Denmark	539	SIR DM 3.8 PM 1.7	ICD-8 hospital discharge diagnoses.. Coupled to life table Cancer registry	No chart reviews were performed to verify diagnosis
Airio[115] 1995 Finland	171 PM 71 DM	SIR DM 6.5, PM 1.0	ICD-7/8 hospital discharge diagnoses. Coupled to life table cancer registry	All cases chart reviewed and classified by P & B
Buchbinder, R[111] 2001 Australia	103 IIM patients	SIR DM 6.0, PM 2.0 sIBM 2.4	Biopsy-proven IIM. Coupled to life table cancer registry	All cases chart reviewed, classification criteria utilized not given.
Stockton[116] 2001 Scotland	286 DM 419 PM	SIR DM, 7.7 PM 2.1	ICD-9 hospital discharge codes, coupled to life table cancer Registry	No chart review performed to verify diagnosis
Limaye V et al[107] 2013 Australia	373	SIR DM 2.2, PM 1.3 sIBM 1.4	Biopsy-proven IIM, coupled to life table cancer Registry	Chart review performed, 80% met P & B

1.1.11 Treatment PM/DM

Before the discovery of corticosteroids, the prognosis and outcome of IIM was poor and associated with high mortality and major disability. Due to the limited number of controlled trials utilizing validated outcome measures and the rarity and the heterogeneity of IIM, the treatment of IIM is complex and challenging.[117] Most treatment regimens are based on case-series, expert opinion and studies without validated outcome measures. International Myositis Assessment and Clinical Studies (IMACS) group, is currently validating measures of disease activity, damage and response to treatment to allow for better drug surveillance and assessment.[118]

Even today, high dose corticosteroids are conventionally used as first-line therapy and the majority of IIM patients at least improve with corticosteroid treatment.[117, 119, 120]. Due to all the long-term side-effects of steroids, the usage of non-steroid immunosuppressive treatment has become the standard level of care over the recent years. Methotrexate and Azathioprine are the drugs of choice as steroid-sparing medication.[121] Recent studies have shown that patients treated initially with azathioprine have better survival.[97, 104]

Cyclosporine and Tacrolimus are sometimes utilized in patients with ILD in combination with corticosteroids.[122-125] Intravenous Immunoglobulins (IVIG) are used in rapid progressive severe myositis, especially when oesophagus is involved.[126-128] MMF, alone or in combination, has been shown successful in some cases in treating refractory PM/DM, also with ILD.[129-131] Cyclophosphamide is usually utilized in patients with severe disease and ILD, but concerns over the development of late malignancies has limited their use over the recent years.[124] One of the few randomized controlled trials on IIM has recently been published on Rituximab treatment.[132] Anti-TNF and Tocilizumab are currently being tested for efficiency and effect in treating IIM patients.

1.2 Sporadic Inclusion Body Myositis (sIBM).

1.2.1 History of sIBM

Sporadic inclusion body myositis (sIBM) was first acknowledged as an entity separate from PM in 1971[133], but descriptions of histopathological and clinical features compatible with sIBM exist from the mid-60s.[134, 135]Traditionally, sIBM has been regarded as one of the three IIM and it may account for 30% of IIM cases.[33, 136] There is, however, growing evidence that the disease mechanisms in sIBM differ from PM and DM, [33] and represent a distinct separate entity with both inflammatory and degenerative changes.[137-140]

1.2.2 Clinical features of sIBM:

This disorder is characterized by slowly progressive, asymmetric, atrophy and weakness of both proximal and distal muscles, most prominently affecting the finger and wrist flexors and quadriceps. [141] Recent, large-sized clinical studies provide further support to the notion that the muscle disease pattern in sIBM is highly characteristic, with asymmetric distribution, slow progression of proximal and distal weakness and predominant involvement of the quadriceps and finger flexor muscles.[137, 142] Dysphagia appears to be very frequent and can be disabling and potentially life-threatening. [22, 23, 137]. Unlike PM and DM, sIBM is unresponsive to immune-modulating treatments. Hence, even though involvement of other organs than muscles is rare, sIBM has an end-stage of major disabilities.[142, 143]

1.2.3 Classification criteria sIBM

Since we do not know the cause or pathogenesis of IBM, there is no “gold standard” for the diagnosis. There is an ongoing debate on how sIBM should optimally be diagnosed. The first widely used diagnostic criteria for sIBM, suggested by Griggs et al. in 1995, were primarily based on histology findings.[144] In 1997, the European Neuro-Muscular Centre (ENMC)

produced new criteria set which allowed for sIBM diagnosis in cases with highly suggestive clinical features, but incomplete histology (Table 7) .[145] Diagnostic criteria primarily based on clinical findings were first proposed by Hilton-Jones in 2009.[146] These criteria only required that histology was supportive, and not inconsistent with sIBM.[146] The new ENMC diagnostic criteria (2011 ENMC IBM Research Diagnostic Criteria)[147] also emphasize clinical phenotype rather than pathology, and additionally, aim to allow for earlier diagnosis than previous criteria sets (Table 8A,B and C).

Table 7. ENMC 1997 criteria [145]

Clinical items	
1	Proximal weakness
2	Distal weakness (forearm muscles, particularly finger flexors, or wrist flexors more than wrist extensors) ¹
3	Slowly progressive course
4	Sporadic disease
5	Age above 30 years at diagnosis
6	Disease duration above 6 months
Histological items	
7	Mononuclear inflammatory infiltrates with invasion on non-necrotic muscle fibres.
8	Rimmed vacuoles
9	Ultrastructure tubulofilaments (protein accumulations) of 16-21nm
Scoring of ENMC criteria;	
	Definite sIBM 1,2,3,4,5,6,7,8 or 1,3,4,5,6,7,8,9
	Probable sIBM 1,2,3,4,5,6,7 or 1,3,4,5,6,7,8

Table 8, Overview of the 2011 ENMC IBM Research Diagnostic Criteria

A Clinico-pathologically defined sIBM

Clinical and laboratory features	Pathological features
1 Duration >12 months	All of the following
2 Age at onset >45 years	1 Endomysial inflammatory infiltrate
3 Knee extension weakness \geq hip flexion weakness and finger flexion weakness > shoulder abduction weakness	2 Rimmed vacuoles
4 Serum CK no greater than 15 \times ULN	3 Protein accumulation or 15–18 nm filaments

B Clinically defined

Clinical and laboratory features	Pathological features
1 Duration >12 months	One or more, but not all of;
2 Age at onset >45 years	1 Endomysial inflammatory infiltrate
3 Knee extension weakness \geq hip flexion weakness and finger flexion weakness > shoulder abduction weakness	2 Rimmed vacuoles
4 Serum CK no greater than 15 \times ULN	3 Protein accumulation or 15–18 nm filaments

C Probable sIBM

Clinical and laboratory features	Pathological features
1 Duration >12 months	One or more, but not all of;
2 Age at onset >45 years	1 Endomysial inflammatory infiltrate
3 Knee extension weakness \geq hip flexion weakness or finger flexion weakness > shoulder abduction weakness	2 Rimmed vacuoles
4 Serum CK no greater than 15 \times ULN	3 Protein accumulation or 15–18 nm filaments

The clinically defined and Probable IBM only require one of the following findings on muscle biopsy; endomysial inflammatory infiltrates, up-regulation of MHC-1, or rimmed vacuoles.

The clinically defined IBM require stricter clinical findings, especially when it comes to definition of distal muscle weakness i.e.: knee extension weakness > hip flexion weakness and finger flexion weakness > shoulder abduction weakness.

The probable IBM diagnosis is the same as the clinically defined IBM, but requires less strict definitions of distal muscle weakness; knee extension weakness > hip flexion weakness or finger flexion weakness > shoulder abduction weakness.

1.2.4 Aetiology and pathology sIBM:

When sIBM was first described, it was also regarded as a primary immune-mediated, but recent data have more suggested that the disease is caused by degenerative processes [148]. In sIBM, clonally expanded CD8 positive cytotoxic T cells invade muscle fibre that express MHC-class I antigens, which leads to fibre necrosis via the perforing pathway and vacuoles formation with amyloid deposits coexisting with the immunological features[2] Muscle biopsy characteristically reveals endomysial inflammation infiltrates and lymphocyte invasion in morphologically normal myocytes and degeneration with small groups of atrophic fibres, eosinophilic cytoplasmic inclusions and muscle fibres with one or more rimmed vacuoles.[149]. However, it is important to note that any given sIBM biopsy may lack any of these characteristic microscopic features. [150]

Genetic studies on the Major Histocompatibility Complex (MHC) have discovered a susceptibility region in the 8.1 ancestral haplotype in a 172 Kb region near the HLA-DRB1*0301 (HLA-DR3) allele. This region contains 3 genes; BTNL2, HLA-DRA and HLA-DRB3.[151] Further studies are ongoing to map the susceptibility gene. However it might be possible that epistatic interaction at this site is important in determining susceptibility, as it appears that the HLA-DR1/DR3 combination is a higher risk for developing sIBM, rather than HLA-DR3 homozygotes.[152]

1.2.5 Epidemiology sIBM

Few studies on the epidemiology of sIBM have been performed. The first, large chart review study on sIBM was a nationwide collaborative cross-sectional study performed in the Netherlands in 1999. [153] The study applied the 1997 ENMC criteria and identified 76 patients with sIBM; giving an estimated population prevalence of 4.9/ 1 000 000. [153] The authors reported that prevalence was probably underestimated, but to date, there are no equivalent European studies for comparison. Three Australian surveys, all based on local histopathology criteria, reported sIBM prevalence ranging from 9.3 to 50.5 per million.[154-156] In Japan, the prevalence of sIBM, judged by the combination of several sIBM criteria sets [144, 146, 150] was estimated to 9.8 per million in 2003, with an increasing prevalence over the last decade.[157, 158] In contrast, a recent biopsy-register study from Turkey reported only 1 sIBM case per million, possibly reflecting differences in sIBM prevalence across genetic backgrounds.[159]

1.2.6 Mortality and morbidity in sIBM.

Knowledge on survival and mortality in sIBM is more limited. Long-term follow-up studies from Europe have not found reduced life expectancy. [160] In contrast, a recent multi-national study on selected patients, with no detailed case definition data available, reported increased mortality, with an estimated SMR of 6.58 for patients aged 41+, and 4.82 for patients over 70. [161] One of the few long-term follow-up studies recently published did not find a higher mortality rate or lower life-expectancy compared to age/sex matched normal background population, but the study did however find different causes of death in the sIBM cohort; mostly related to infection, respiratory complications-aspiration, cachexia and malnutrition and a higher incidence of cardiac associated deaths.[142] The study concluded that the outcome in sIBM is one of major disabilities at the end stage of the disease due to extensive

muscle weakness[142] The mean decline in strength was 3.5 and 5.4% per year according to the manual muscle testing and quantitative muscle testing, respectively. This decline was most pronounced in the lower legs, which were also the weakest extremities. Life expectancy was normal at 81 years, but activities of daily life were clearly restricted. At follow-up, all patients were found to be using a wheelchair, 47% being completely wheelchair-bound.[142]

1.2.7 Cancer risk sIBM

Population-based retrospective cohort studies have consistently confirmed an increased risk of malignancy in the setting of DM and PM and recently in sIBM. A recent retrospective study on biopsy-proven IIM cases from Victoria, Australia reported increased cancer risk across all IIM subsets, including sIBM (Table 6). This study found the proportion of sIBM patients having cancer to be 23% and the SMR 2.4 CI 95% (1.4, 49) [111] There are in addition several case-rapport supporting these findings [162-164] On the other hand, a 12 year long-term follow-up study from the Netherlands did on the contrary find a smaller incidence of malignancy in the sIBM cohort compared to the background population.[142]

1.2.7 Treatment sIBM

To date no efficient treatment of sIBM exists, there are however possible promising new drugs being tested.[165, 166] There is also no standard course of treatment. The disease is generally unresponsive to corticosteroids and immunosuppressive drugs.[137, 167-173] Some evidence suggests that intravenous immunoglobulin may have a slight, but short-lasting, beneficial effect in a small number of cases, but the effect has not been shown to sustain over time.[169, 174-179] Physical therapy may be helpful in maintaining mobility. Other therapy is symptomatic and supportive.

2. AIMS of the study:

Main aim:

To establish baseline estimates of the occurrence, disease characteristics, survival and cancer risk in IIM patients in South-east Norway in the period from 2003-2012.

Specific aims:

- Determine the point prevalence and clinical characteristics of a large unselected PM/DM cohort.
- Determine point prevalence and clinical characteristics of sIBM in Southeast Norway by 31.12.2012
- Determine the overall survival of the IIM patients living in Southeast Norway 2003-2012. And to identify the causes of death and mortality hazard ratios.
- To identify the cancer association and risk in all IIM patients

3. Methodological-considerations:

3.1 Study population and data collection:

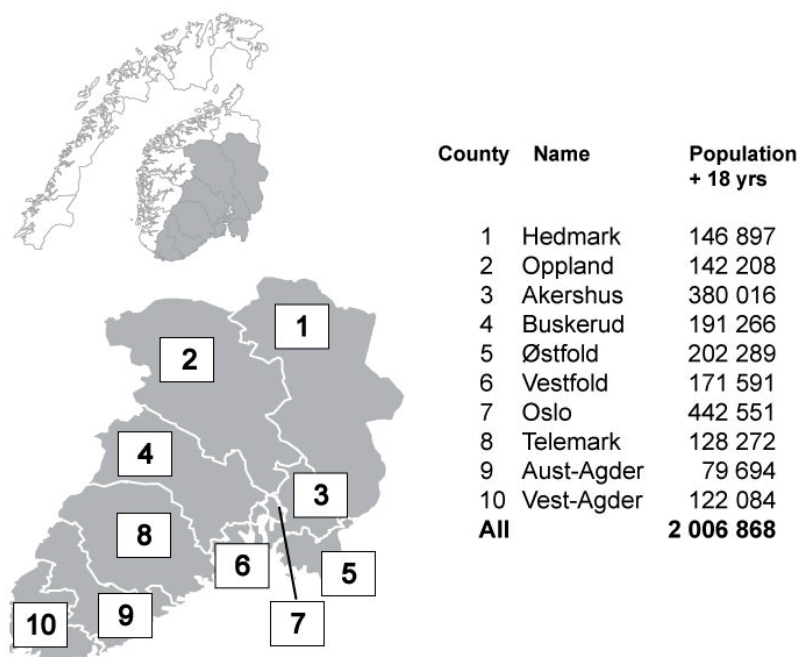
Norway is divided into five health-regions. The largest region is situated in South-east Norway and consist of 10 counties with 2 642 246 inhabitants (by 31.12 2012) and includes the largest cities in Norway and is mostly urban/suburban dwellings (Figure 1). There are 10 main hospitals in the South-east health region; of which Oslo University Hospital (OUH), is the largest and serves as the primary hospital for the whole of Oslo (with 600 000 inhabitants) and tertiary referral centre for all the 10 counties in the region.

In Norway, patients with connective tissue diseases, including IIM are followed by the secondary health system at public hospitals. PM/DM patients are mostly cared for by rheumatologists, and sIBM are seen by either neurologists and/or rheumatologists. Since 1999, all patients contacts in the secondary health system were electronically registered by 10th revised version of the International Classification of Disease (ICD-10) codes. The IIM cohort was selected from this denominator population and consisted of every person who fulfilled the study inclusion criteria for PM/DM and sIBM (see below).

The South-east Norway health region was selected as the denominator population for this IIM-study, due to several factors. Firstly it is the largest health region and consists of approximately half of Norway's population. Hence it produced a large-sized, unselected PM/DM cohort. Secondly, Oslo University Hospital (OUH) is the only specialized centre for connective tissue diseases and vasculitis in Norway, and it has the main focus on IIM in Norway. We therefore believe that most of the PM/DM patients have been referred at least once to this tertiary centre. This fact is confirmed by all intermediary analyses which show that almost all the PM/DM patients in the study cohort were captured more than once, either at more than one site (i.e. locally and at the OUH referral centre) and/or at more than one time

point during the study period. Thirdly, due to labour-intensive approach we utilized and the fact that the approach was very time-consuming and involved all departments at all hospitals in the health region, we did not have the capacity to assess the whole of Norway. But we do believe that South-east Norway cohort gives a good and sound estimate and picture of the IIM patients in Norway. We chose to screen all patients registered with relevant ICD-10 codes at least once in the period from January 2003 to December 2012. The rationale behind this long acquisition period was for patients to have enough time to develop a full clinical picture. We found this especially important in the sIBM cohort, which has an insidious nature and slowly developing clinical picture.

Figure 1 Map over South-east Norway and its 10 counties



3.2 Study inclusion criteria PM/DM:

We decided to include two sets of PM/DM criteria; the Peter & Bohan and Targoff criteria (Table 9). The Peter & Bohan criteria were selected because they are still considered “gold standard” for PM/DM and the basis for much of previous IIM research. We did in addition include the Targoff criteria because they also include MRI and MAA criteria and has recently been evaluated to be the most sensitive of existing IIM criteria.[37] A limitation with the Targoff criteria is that early PM cases without all typical biopsy, EMG or MRI findings may be missed out and the patients may not fulfil the criteria at the first visits. Moreover, the Targoff criteria require many tests to be performed, which could lead to an underestimate of the prevalence due to missing data. The first limitation was tried overcome by having a long acquisition period. The rationale for exclusion of overlap syndromes is the wish to look at pure IIM patients. There are existing Systemic Sclerosis, MCTD and SLE cohorts at OUH being looked at separately.

Table 9 Study inclusion criteria PM/DM

A	Disease classifiable as probable or definite adult PM or DM by the Peter & Bohan criteria and/or the Targoff criteria [27, 28]
B	Age above 18 years at disease onset.
C	Registered in the Norwegian Central Register with a home address in South-east Norway between January 1 st 2003 and December 31 st 2012.
D	Myositis not explained by the presence of another connective tissue disease (i.e. SLE, Systemic Sclerosis or Mixed Connective Tissue Disease).

3.3 Study inclusion criteria sIBM:

There is an ongoing debate on how sIBM should optimally be diagnosed .We chose to utilize the 1997 ENMC criteria (Table 7). The rationale behind this, was that the 1997 ENMC criteria was the only one that had been utilized in the previous European epidemiological sIBM study that exists.[153] The 1997 criteria was also one of the first criteria to allow for sIBM diagnosis in cases with highly suggestive clinical features, but incomplete histology .[145] The new ENMC diagnostic criteria (2011 ENMC IBM Research Diagnostic Criteria)[147] (Table 8 A, B and C) was published in 2013 after the end of the study inclusion. The new criteria emphasize clinical phenotype rather than pathology, and additionally, aim to allow for earlier diagnosis than previous criteria sets. We found it interesting to assess and compare these two sets and to validate the new criteria. But there were difficulties and limitations due to the retrospective assessment of the 2011 criteria. The problems were mostly related of the incomplete data and missing information on muscle power, function and testing. Not all patients had been assessed by Physiotherapists for Manual Muscle Tests (MMT) or Functional Index 2 (FI2) or MRC (Medical Research Council) scale by neurologist. We did have information about distal muscle involvement, but not always which specific muscles that were affected. This led to that most patients were classified as probable sIBM (table 8 C).

Table 10; Overview of study inclusion criteria for sIBM

A	Disease classifiable as sIBM by the 1997 ENMC sIBM criteria, and /or the 2011 ENMC IBM Research Diagnostic Criteria.[145, 147]
B	Exclusion of PM or DM as possible diagnoses
C	Inclusion body myositis not explained by familial disease.
D	Patient registered in the Norwegian Central Population Register with a home address in South-East Norway between January 1 st 2003 and December 31th 2012

3.4 Case finding strategy:

Two major acquisition routes were utilized to identify all the adult PM/DM and sIBM patients (1) extensive searches across multiple ICD-10 codes (Table 11) to catch all potential IIM patients, followed by chart review of all of the encoded patients (2) and for sIBM patients retrospective review of all muscle biopsy reports that had been encoded with inflammation. We applied a wide range of relevant ICD-10 codes, over a long acquisition period, to ensure that all the IIM cases living in the study area were captured (Table 11). The rationale behind the chosen ICD-10 codes were to also catch sIBM patients which do not have a separate ICD-code. Initially, the database at OUH was screened across all the ICD-10 codes selected (Table 11): [180]. The OUH data showed that no sIBM cases were given G-codes. Only one PM patient received a G-code (G72.9), but this patient was diagnosed in 1993. Hence, the searches undertaken at the other South-East Norway hospitals, was limited to the six M33 and M60 codes.

Table 11, ICD-10 codes utilized in IIM search

ICD-10 code	Description	ICD-10 code	Description
M33.1	Adult DM	G72.4	Inflammatory myopathy, not specified
M33.2	PM	G72.8	Other specified myopathies
M.33.9	Unspecified PM/DM	G72.9	Unspecified myopathy
M60.1	Interstitial myositis	G73.7	Myopathy associated with diseases classified elsewhere
M60.8	Other, specified myositis		
M60.9	Unspecified myositis		

For the sIBM part of the study, all muscle biopsy reports obtained between 2003 and 2012 were re-reviewed. These muscle biopsies were initially examined by five neuropathologists at two laboratories in Oslo (Rikshospitalet and Ullevål) and one in Tromsø. From 2010, the two laboratories in Oslo were merged within the Department of Pathology, OUH. For our review, all the muscle histology reports encoded with inflammation in the Systematic Nomenclature of Medicine (SNOMED) code system were reviewed by a neuropathologist (EAA), and the following parameters were recorded; endomysial inflammatory infiltrates, lymphocyte invasion in vital myocytes, rimmed vacuoles, MHC 1-expression (any and general), and the presence of inclusion body filaments at ultra-structural examination. The neuropathologist had access to muscle biopsy referral information and the pathology reports produced by the five other neuropathologists, but not the clinical charts and patient journals.

3.5 Patient characteristics and disease measures:

Predefined registration forms were used to record hospital chart data on the patients identified by the ICD-10 based case finding strategy. All information was imported to the Microsoft Office Access database after scanning with Cardiff Teleform 10.1 Software.

Age, gender, time of symptom onset, time of disease onset (defined as the date when IIM was first diagnosed) and patient observation period was recorded. The observation period was terminated 31st of December 2012 or at the time of death. Disease duration was defined as the time from diagnosis to the end of the observation period (Table 12).

Table: 12 Demographic variable and disease characteristics

Date of birth, first and last name and gender
Residential town and county
Diagnosis ICD-10 and name of diagnosis (PM, DM, sIBM or unspecified)
Date of first and last hospital contact and name of hospital
Year of first symptoms
Year of diagnosis
Date of death and cause of death
Data source (hospital and ward)

Clinical parameters were recorded at disease onset and cumulatively during follow-up (Table 13). ; The myalgia frequency were scored as positive when a doctor reported it as an observed sign or as a subjective symptom by the patient. The interpretation of this symptom is subjective and may have led to an overestimation, especially due to retrospective design and interpretation of subjective data by, in many cases, a single observer. Arthritis needed to be confirmed by doctor; either clinically, by ultrasound or MRI imaging.

The following laboratory parameters were also recorded; ESR (Erythrocyte Sedimentation Rate), anti-nuclear antibodies (ANA), MAA (anti-Jo-1, anti-PL-7, anti-PL-12, anti-SRP and anti-Mi-2) and anti-SSA. Imaging data and functional lung and heart data were recorded (Table 14) We also recorded data on the following immune-modulating treatments; corticosteroids, Methotrexate, Cyclophosphamide, Cyclosporine A, Rituximab, intravenous immunoglobulin, Mycophenolate mofetil, Tacrolimus, Hydrochloroquine and anti-TNF treatment. Treatment was recorded as received, not received or missing data. All available chart data on malignant disease, at any time during the life of the patient, was also recorded.

Table.13 Clinical parameters recorded at debut and during follow-up. Parameters were recorded as present, absent or missing data.

Symptoms	Symptoms and other chronic diseases
Arthritis / Arthralgia	Dyspnoea
Mechanical hands	Cough
Dysphagia	Muscle weakness
Calcinosis cutis	Myalgia
Gottrons signs/ rash	Fever, “flu-like symptoms
Heliotrope rash	Cancer
Sicca phenomenon	Heart disease
Raynaud	Pulmonary disease not related to IIM
Other connective tissue disease or chronic disease	

Table.14 Imaging and investigations recorded as present, absent or missing data:

Plain radiology of the lungs	Present/absent or missing data
High Resolution Computed Tomography of the lungs (HRCT thorax)	Date of first HRCT thorax, date of first sign of ILD, date of last HRCT thorax undertaken
Dynamic studies of the Oesophagus	Date of examination(s) Dysmotility: yes/no/missing data
Pulmonary function testes	Date of last examination. FVC, FEV1, DLCO in numbers and percentages
Echocardiography	Pathology; yes/no
ECG	Pathology; yes/no

3.6 Recording of patient data and items assessed by the Targoff criteria:

Detailed recording of the P&B and Targoff criteria items was performed. Items were defined as positive by the following rules; (1) Proximal muscle weakness: described by a specialist (rheumatologist or neurologist) during clinical examination as weakness (and sometimes weakness) involving thigh and/or shoulder/neck muscles. Weakness was sometimes also quantified by the Medical Research Council (MRC) scale (0-5) and/or Manual Muscle Testing (MMT) performed by physiotherapists. (2) Elevated serum muscle enzymes- creatine kinase (CK) ,(3) EMG/neurography described as myopathy by neurophysiologist. (4) muscle histology compatible with IIM (5) typical DM rash- Gottrons papules or sign and/or Heliotrope rash. (6) Positive MAA (anti-Jo-1, anti-PL-7, anti-PL-12, anti-SRP and anti-Mi-2) by immune blotting or ELISA. (7) muscle MRI findings compatible with myositis, as described by a radiologist. We chose to register a large number of clinical information and

patient characteristic in order to map most of the clinical characteristics and outcomes as possible. To obtain the DM diagnosis the patient needed to have descriptions of a rash recorded by a doctor compatible with Gottron's papules or sign and/or Heliotrope rash. In our study we did not have any patients that only exhibited V or Shawls signs alone without Gottrons signs/papules or Heliotrope rash. Patients with a muscle biopsy compatible with DM without a skin rash, was not classified as DM and patients with a muscle biopsy compatible with PM, but with Gottron's sign or papules and/or Heliotrope rash were classified as DM.

Retrospectively, we wish that a more detailed description of muscle power had been noted and defined. But unfortunately this study has a retrospective design and hence has several weaknesses in that data collection is undertaken on medical records and not by standardised definitions. We did gather a lot of radiological and treatment data, which has not yet been analysed. These data will be handled in the near future.

. 3.7 Recording of patient data and items assessed by the 1997 and 2011 ENMC criteria for sIBM.

Scoring of the clinical and histopathology items according to the 1997 and 2011 ENMC criteria was performed as follows (Table 14); (1) Proximal muscle weakness: described by a specialist (rheumatologist or neurologist) during clinical examination as weakness (and most often also atrophy) involving thigh and/or shoulder/neck muscles. Weakness was quantified by the Medical Research Council (MRC) scale (0-5) and/or Manual Muscle Testing (MMT) performed by physiotherapists. (2) Distal muscle weakness: described by a specialist during clinical examination as weakness in the finger flexors and/or the combined presence of reduced grip strength and atrophy of ulnar forearm muscles. Distal weakness was not quantified, but registered as present or absent. (3) Knee extension weakness, described by a

specialist and quantified by MRC and/or MMT. (4) Slowly progressive course; chart description of weakness progressing slowly over years. (5) Sporadic disease; no chart information on familial clustering. (6) Total disease duration over 12 months. (7) Age of onset; above 30 years for 1997 criteria and above 45 for 2011 criteria. (8) Maximum CK levels, recorded from chart data. (9) Muscle biopsy parameters recorded from pathology reports; endomysial inflammatory infiltrates, lymphocyte invasion in vital myocytes, rimmed vacuoles, MHC 1-expression (any and general), the presence of inclusion body filaments at ultra-structural examination.(Table 14). The ENMC criteria include protein accumulation staining (p62, Congo red, TDP-43), unfortunately only a simple Congo stain are available at the pathology departments involved. Simple Congo stain does unfortunately not have a great place in the search for inclusions (probably not sensitive enough). This may have led to an underestimation of inclusion body filaments at ultrastructure examination.

OUI, Rikshospitalet, uses a routine diagnostic process, involving sectioning large quantities of deeper sections from the frozen tissue (in search for inflammatory infiltrates and rimmed vacuoles). This may have influenced the number of rimmed vacuoles found in each biopsy. In addition, toluidine blue stained sections from glutaraldehyde fixated muscle, are also routinely examined by light microscopy, which may also have improved the chance of finding rimmed vacuoles. Unfortunately, we did not formally record the number of sIBM patients that were initially diagnosed as PM or unspecified myositis, but our impression from the chart review process was that approximately 1/5 of the sIBM patients had another myositis diagnosis before they were diagnosed with sIBM.

3.8 Assessment of Standard mortality rate (SMR) and survival rates:

Every IIM patient was matched with 15 healthy controls drawn from the national population registry via Statistics Norway. The matching included the same sex, area of residence, month and same year of birth. Vital status at January 1st, 2013, was provided for patients and controls by the National Population Registry. Causes of death were obtained from the Cause of Death Registry, coded with ICD-codes, in addition patients journals were searched for death certificates and clinical information in addition to autopsy reports. The case-control approach to survival analysis in IIM has not been utilized previously, and we found it interesting to assess the accuracy, compared to that of life-tables. When matching controls from the national population registry via Statistics Norway, we encountered problems with the identity of two patients which had been operating with two different names and personal identification numbers. We decided to exclude these all together from the last study, leading to a total of 326 IIM patients included in the survival and cancer-research.

3.9 Assessment of causes of death:

Using the personal identification numbers, we were able to identify every diseased person and all the reported causes of death in the IIM cohort between 01.01.2003 and 31th of December 2012. Causes of death were identified by manual chart review of medical charts, death certificates and autopsy and from codes from the Cause of Death Registry. When there was discrepancy between information, data from the medical charts were used. The cause of death in the control group was given by Statistics Norway. In the IIM group causes of death was classified as either as IIM related mortality or mortality unrelated to IIM. If there was no notification of the death-it was named unknown.

3.10 Assessment of Cancer in IIM cohort.

The cancer registry, Norway provided data on cancer prevalence between 2003-2012 in the IIM patients and their matching controls, coupled via their personal identification numbers. Time and place of cancer diagnosis, stage, type and metastasis, organ of origin, and if death was related to cancer. Eight additional patients had received cancer diagnosis before 2003 and were identified during chart review and pathology reports. We included the latter eight to enable for the assessment of disease-related cancer \pm 3 years the year of diagnosis. The rationale for usage of 15 controls pr. patient was to have the most precise control group to compare, and we did not use life-tables. But when it came to rarer cancer-forms, with low prevalence in the population, we utilized life-tables in addition, to ensure a correct estimate.

3.12. Statistical analysis.

Statistical analysis was undertaken by SPSS, version 20/21 and STATA[181]. Descriptive statistics; continuous variables with normal distribution were presented as mean with Standard Deviation (SD) or 95% Confidence interval. Categorical variables were presented as numbers and percentages. Group differences were analysed by Student t-test (2-tailed, unpaired). Pearson's Exact test and Chi Squared test was utilized for the comparison of independent groups of categorical data, significance level was $p < 0.05$. Cumulative survival rates were calculated by the Kaplan-Meier method and significance was tested with the log-rank test. Survival curves were used to compare with the curves of the controls. Hazard rates were calculated by usage of SPSS Cox regression, survival and hazard plots. STATA was utilized when calculating SMR and SIR, and Incidence rate ratio, SMR pr. 1000 person year. Mean time to death in years and Mean time from cancer to death in years were calculated using SPSS and STATA. STATA was also used when calculating 2,5 and 10 year survival.[181]

3.13 Legal and ethical aspects:

The Regional Committee of Medical ethics in Southern Norway (REK sør), the Norwegian Ministry of Health (the Norwegian Patient Registry) and Privacy Policy Department at OUH have all approved this study with all aspects related to patient data recording and ethical aspects related to the handling of patient sensitive material.

4. Summary of results:

Paper 1:

Prevalence and clinical characteristics of adult polymyositis and dermatomyositis; -data from a large and unselected Norwegian cohort

In this study we aimed at identifying all PM/DM cases over a 10 year period and to calculate the point prevalence on the 31st of December 2012. Furthermore; we wanted to map the clinical characteristics of the PM/DM patients identified and to compare the two patient groups. All hospitals in South-east Norway were screened for potential IIM-patients by ICD-10 code searches.

The total number of cases identified by the code search was 3160. Manual chart review revealed that, only 230 of these 3160 cases met the Targoff criteria (130 DM and 100 PM.)

The point prevalence of PM/DM was estimated to be 8.7/ 100 000 (CI 95% 4.5, 11.2) with large variations seen between the counties. Calculated annual incidence rates based on retrospective data with their limitations ranged between 6/1 000.000 and 10/ 1000.000 across the study period. .

The peak incidence for PM patients was between 60-69 years compared to 50-59 in the DM group. At diagnosis, the mean age of the PM patients was 56.0 years, higher than the mean 51.6 years in DM. Mean time from symptom debut to diagnosis did not differ between the groups, but diagnostic delay above two years was more frequent in PM (29%) than in DM (14%), ($p=0.005$).

Chart information about clinical features at disease onset and during follow-up was recorded and cumulative frequencies estimated. Muscle weakness was present in 84% at disease onset and cumulatively in 97%. Dysphagia was quite rare at disease onset (23%), but increased to 58% during follow-up. Dyspnoea, Raynaud's phenomenon and mechanic hands were more frequent in DM than in PM ($p = 0.002$, $P=0.009$ and $p=0.0000$ respectively). We found that

DM patients had more extra-muscular features than PM. Pathological MRI findings were noted in 137/163 (84%) of the patients,

MAA was identified in 59% of DM patients and 41% of PM patients. The most commonly tested and detected MSA was anti-Jo-1, being present in 65/204 (28%) of the patients, 47/121 (39%) in DM and 18/83 (22%) in PM. Correlation analyses showed correlations between anti-Jo-1 and dyspnoea (unadjusted Odds ratio (OR) 7.7) arthritis (OR 7.5) and mechanic hands (OR 4.5).

In conclusion, this study provides novel population-based data on the prevalence and clinical characteristics of PM and DM in Caucasians. Compared to previous studies, the prevalence and incidence rates are similar, but more strikingly are the number of anti-Jo and MAA positive patients in this cohort.

Paper 2

High prevalence of Inclusion Body Myositis in Norway; a population based clinical epidemiology study.

In this study we aimed to identify all sIBM patients in south-east Norway and to calculate point prevalence on the 31st of December 2012. We did in addition want to assess clinical characteristics, gender differences and differences in follow-up-regimens and to assess imaging data. The ICD-10 based case finding and chart review process was done in conjunction with PM/DM (Paper 1). In addition, a review of all muscle biopsies encoded with inflammation was performed by an experienced neuropathologist. All the potential sIBM cases identified were scored according to the 1997 ENMC criteria and later by the 2011 ENMC criteria. Patient chart review and muscle biopsy reports showed that 100 of the patients identified by the case finding strategies met either the 1997 and/or the 2011 ENMC criteria for sIBM. The 1997 criteria were met by 92 patients, while 95 met the 2011 ENMC criteria. Retrospective chart review showed that all the patients had proximal muscle weakness and knee extension weakness. Distal weakness (i.e. finger flexor weakness) was described in 94/100 patients. The most frequent biopsy features were endomysial inflammatory infiltrates (in 92/97 patients) and rimmed vacuoles (91/97). Up-regulation of MHC 1 (of any degree) was described in 78/95 patients, with generalized MHC1-up-regulation in 61 biopsies. Electron microscopy was performed in 70 patients, and 16 of these had 15-18 nm tubulofilaments.

At diagnosis, the mean age of sIBM patients were 66.9 years, and mean time from symptom onset to diagnosis was 5.6 years. Male to female ratio was 1.5:1. Clinical characteristics showed no gender bias, except from dysphagia, being more common in women (94 %) than in men (65%). Serum auto-antibodies were frequent; with ANA in 37% and anti-SSA in 22%; with a female predominance.

The estimated point prevalence of sIBM in South-east Norway by the 1997 and 2011 criteria were thus similar at 33/1.000 000 and total 35/100 000 for the entire cohort on the 31th of December 2012. Large differences between the individual counties in the area were noted. Estimated annual incidence rates of sIBM across the study period ranged from 2/1 000 000 to 6/1 000 000. We identified that 24% of patients exhibited co-existing rheumatic diseases (24%), most commonly Sjögren`s syndrome (10%) were exclusively followed by rheumatologists..

MRI of thigh muscles had been undertaken in 56/100 patients, and 88% had atrophy and oedema. Oesophageal dysmotility was recorded in 45/54 patients examined by this modality. In conclusion, we found a point prevalence of sIBM 7 fold higher than previous epidemiological studies from Europe, which may indicate that there might be an underestimation of sIBM in Europe and that there possible is a genetic link to this disorder.

Paper.3

Survival and cancer risk across an unselected and complete cohort of idiopathic inflammatory myopathy in south-east Norway.

In this paper, the PM/DM and sIBM cohorts described in Paper 1 and 2 were utilized for mortality and cancer risk analyses. The 326 IIM patients included (98 PM, 128 DM and 100 sIBM) were matched to 15 controls with same the age, gender and residential area. The cohort and controls were coupled to the Causes of Death registry, Statistics Norway and Cancer Registry Norway. By the end of the study period, 87/326 patients had died. Mean time from diagnosis to death was shorter in DM (4.2 years) than in PM and sIBM.

Mortality was primarily assessed by SMR. The highest SMR (2.6) was observed in DM. Stratification by time of diagnosis showed that SMR was significantly lower in DM patients diagnosed before 2003 (SMR 1.3) than in patients diagnosed from 2003 and onwards (SMR 3.2). The same trend was seen in PM. Survival rates was calculated by Kaplan Meier Graphs and the test of equality of survival distribution verified that the survival of IIM patients were lower than that in matched controls (Log Rank (Mantel Cox) ($p < 0.000$).

2,5 and 10 year cumulative survival was also calculated separately by STATA. The most sticking differences were seen at 10 years, where sIBM appeared to have a poor outcome with 42% cumulative survival, but the corresponding low survival in the matched controls show that this was an effect of old age at diagnosis. DM patients had a 55 % 10 year survival and the lowest age at diagnosis compared to 78% in their matching controls, compared to PM with 60% 10 year survival and 82% in controls.

Causes of death were related to IIM in 56/87 (64%) patients. In DM, nine patients died secondary to myositis-associated cancer compared to five and three in PM and sIBM, respectively. ILD/PH caused nine deaths in the DM group compared to none in the sIBM

group and five in the PM group. Aspiration associated deaths were mostly seen in sIBM. Mortality risk factors, calculated by Cox regression, found that mean age at diagnosis was associated with increased mortality across all three IIM subsets. Disease duration was protective in all patients ($P=0.000$), with a lower risk in patients surviving past the first years of diagnosis. Cancer was identified as a risk factor in all IIM subsets, with hazard rates (HR) of 9.0 ($P=0.000$) in DM, 2.7 in PM ($P=0.013$) and 2.5 in sIBM ($P=0.025$). Diffusing capacity for carbon monoxide (DLCO) $<60\%$ (a marker for pulmonary involvement) was associated with a 13 fold risk in PM patients and a 5 fold risk in DM patients. In DM, FVC $< 70\%$ was also associated, with HR 7.0. The frequency of anti-Jo-1 was very high in our cohort, but neither anti-Jo-1, nor MAA in total were associated with increased HR.

Total frequency of cancer in the IIM cohort was 24% compared to 16% in the age- and gender matched controls. Standard Incidence ratio (SIR) for cancer was higher in DM (2.0) than in PM (1.3) and sIBM (1.0). Myositis associated cancers, defined as occurring ± 3 years of diagnosis, were seen in 18 DM patients and 11 PM patients, with a large peak at the same year as IIM diagnosis. Cancer types and frequencies differed between the disease groups. The most frequent encountered cancers in DM were lung and ovarian cancer. In PM, haematological malignancies were the most common cancer types.

These findings show a higher mortality and cancer-association, especially in DM patients, but also in PM. There are high numbers of disease related deaths in this cohort, some of which are potentially preventable.

5.0 Discussion:

5.1.1 What is the role of epidemiologic research in IIM?

In the recent years, the main focus of research in the field of IIM has been on genetic studies and molecular studies on Myositis Associated Autoantibodies (MAA). Updated and valid epidemiologic data about the true incidence, prevalence and mortality are still missing in most parts of the world. The difficulties that exist in the epidemiology of IIM are due to the rarity of the diseases, heterogeneous study populations and difficulties with classification.[1, 29, 75] The epidemiological studies to date are few in numbers and mostly undertaken in single centres on selected patients. The importance of epidemiological research should not be undermined, and their role is to establish the fundament for all clinical research and more basal scientific studies. Genetic studies and molecular research can never substitute clinical knowledge and data on occurrence and the outcome of IIM. Hence, we believe that epidemiology is imperative in the understanding of the mechanisms of disease.

5.1.2 What have our methodology approach taught us?

Our approach, we believe, differs some from previous IIM epidemiology studies on several important issues. We would like to highlight four points that may have influenced the results we obtained;

1) The case finding strategy; we applied a wide range of relevant ICD-10 codes, over a long acquisition period, to ensure that all IIM cases living in the study area were captured. In the next step, which we think was absolutely critical, we performed data collection and reviewed all journals that met the ICD-10 codes involved. Notably, the recently published database studies, solely based on code-searches,[81, 82, 182] would in our case, most likely have increased the number of IIM cases dramatically. In fact, of the 3160 patients identified by our code searches, only 328 met the inclusion criteria. The sIBM study was undertaken in conjunction with the study on the other IIM (PM and DM), which gave us the opportunity to

search for sIBM, which does not have a specific ICD-10 code, across a wide range of relevant myositis and myopathy codes; and it forced us to actively select against the possibility of PM and/or DM diagnoses in every potential sIBM case. Reassuringly, intermediary analyses showed that almost all the IIM patients in the study cohort were captured more than once, either at more than one site (i.e. locally and at the OUH referral center) and/or at more than one time point during the study period. Finally, the frequency of missing data in the cohort was very low.

2) *The use of several classification criteria;* we applied more than one set of classification criteria for all the three diagnoses. In PM/DM, patients were classified by the gold standard Peter and Bohan in addition to Targoff to encompass MRI and MAA findings. By comparison, the Targoff criteria, increased the overall number of classifiable patients only by 10%, but the frequency of definite cases were raised by 30%. In sIBM patients we utilized the 1997 and recently published 2011 ENMC criteria, which had similar sensitivities, but did not capture exactly the same patients.

3) *The use of matched population controls for cancer and mortality analyses.*

These issues were approached by a cancer and mortality design with cases from unselected PM, DM and sIBM cohorts matched with controls of the same age, gender and residential area. Our mortality and cancer data captured by manual chart review was confirmed and extended by data sets from the Norwegian Cancer and Mortality Registries. With the use of 15 age- and sex-matched controls pr. patient, instead of life-tables, we got a unique opportunity to directly compare data across all the mortality and cancer analyses. We did however also look at life table-statistics for rarer cancer-types.

4) *The Norwegian Health system, demographics and genetic homogeneity of the population;* our study has the main advantage that the Norwegian health system is ideal for epidemiological studies; by means of the Personal Identification Number that every Norwegian citizen receives. This means that there is no loss to follow-up in the population. The hospital care also has electronic data journals and good registries for Cancer and Causes of death. The Norwegian population is in addition small, approximately 5 000 000, with only 10% of the population on non-European ancestry, which gives a very homogenous ethnicity, and the environment and climate is distinct and different from most other countries in the world. These properties give a good opportunity to get reliable and sound epidemiologic data and the possibility for novel knowledge due to the homogeneity of the population.

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5.1.3 Have our findings added new knowledge on IIM?

In paper I; we found that the mean age of the PM patients at diagnosis, was 56.0 years, higher than the mean 51.6 years in DM. We have considered that maybe some PM patients in reality suffer from sIBM due the higher mean age at diagnosis and peak incidence, but due to the long follow-up period, we believe that most patients were given the right diagnosis. We found that Pathological MRI findings were noted in 84% of the patients, while positive MSAs were identified in 59% of DM patients and 41% of PM patients. And hence give the impression that MSA and MRI findings are important tools in diagnostics of PM/DM. The most commonly tested and detected MSA was anti-Jo-1, present in 28% of the patients, 39% in DM and 22% in PM, these numbers are different from previous studies were anti-Jo-1 is more prominent in PM patients. We speculate in that our choice of DM definition, may have influenced this number, because patients with muscle biopsies compatible with PM with a rash, were given DM diagnosis if the rash was Heliotrope and/or Gottron`s. The observer

may also have interpreted the rash associated with ASS as DM, a mislabelled the patient. However the results are interesting.

In Paper 2;

In our sIBM cohort, detailed review of the patient charts and muscle biopsy reports showed that 100 of the patients identified by the case finding strategies met either the 1997 and/or the 2011 ENMC criteria for sIBM. The 1997 criteria were met by 92 patients, while 95 met the 2011 ENMC criteria. The patients that were excluded from the 2011 criteria set were all under the age of 45 at diagnosis and the eight patients that did not fulfil any of the 1997 criteria sets, had rimmed vacuoles, but not endomysial inflammatory infiltrates. The differences in numbers of patients fulfilling the criteria sets were not large, but it could be argued that the 2011 criteria would benefit from lowering their age limit at debut. Notably, 79 of the 100 sIBM patients would have met the original Griggs criteria.

Serum auto-antibodies were frequent in sIBM; with ANA in 37% and anti-SSA in 22%; with a female predominance. The results indicate that an immunological process is involved. We found a higher frequency of dysphagia amongst the female sIBM patients. The differences in symptoms of dysphagia may be subjective. We did not correlate these to radiological findings, which would have been a more objective way of measuring this.

Our observations show a much higher prevalence of sIBM than previously described and may support the notion that sIBM is genetically influenced. The large differences seen between the counties may indicate that there still are some patients that remain undiagnosed, possibly reflecting different density of specialists.

We identified that 24% of patients exhibited co-existing rheumatic diseases (24%). This indicates that patients with sIBM should be screened for other rheumatic diseases, especially

Sjögren, because these patients may have a different course of disease and response to treatment.

The high number of findings on patients examined by MRI and radiological studies of the oesophagus, may indicate that these imaging modalities are useful in investigating this disorder,

In paper 3: Causes of death were related to IIM in 56/87 (64%) patients. The main causes of disease-related deaths were cancer, ILD and/or secondary PH in PM/DM and oesophageal associated deaths in sIBM. The findings indicate that screening for cancer, pulmonary complications and oesophageal involvement are vital. And that some of the deaths are potentially preventable. When calculating hazard ratios, disease duration was protective in all patients ($P=0.000$), with a lower risk in patients surviving past the first years of diagnosis. These findings indicate that the majority of deaths occur during the first years after diagnosis. And this point should be elaborated and kept in mind in newly diagnosed patients. Myositis associated cancers, defined as occurring ± 3 years of diagnosis, were seen in 29 IIM patients, with a large peak at the same year as IIM diagnosis. Cancer types and frequencies differed between the disease groups. These findings show a cancer-association with DM and PM diagnosis and that the cancer types these patients encounter, are different to the matched control population. We do not see a clear cancer association in sIBM patients. We do also want to mention that utilizing ± 3 year of diagnosis time window for sIBM patients, may be misleading, because of the diagnostic delay of 5.6 years seen in this cohort. But the symptom debut is hard to define due to the insidious nature of this disease.

5.1.4 Will serology-defined phenotypes replace the traditional PM/DM classification?

During the recent years discovery of several new MAA has become potential tools to aid diagnosis, prognosis and therapeutic considerations in patients with IIM.[183, 184] The novel MAA are still being tested and their complete role is yet unknown. There is a debate that these can be utilized as tools for subgrouping patients and for better understanding of prognosis and outcome. Approximately half of the patients in our IIM cohort, have recently participated in the testing of novel MAA (Sanner et al, unpublished data). Testing of sera with two myositis line immunoassays were undertaken on juvenile dermatomyositis patients (JDM, n=68), adult IIM patients (n=152), disease controls (n=123) and healthy controls (n=30). The two immunoassays; A1 covering six recently discovered MAAs (MDA5, TIF-1g, NXP2, SAE1/2, HMGR and Mup44), and assay A2 with established MAAs (Jo-1, PL-7, PL-12, EJ, OJ, SRP, Mi-2, PMScl 75/100 and Ku) were utilized. Results show that all the six recently described MAA were recognised by adult IIM . Positive response to one or more A1 antigens was identified in 18% (27/152) of adult IIM , while A2 assay responses were seen in 62% of adult IIM. In adult IIM, anti-Mup44 was present in 6/19 patients (32%) with inclusion body myositis and 5/42 Polymyositis patients, three of these five were >70 years and therapy resistant. Anti-HMGR was positive in four adult IIM (one with previous statin exposure). Three adult IIM had detectable anti-NXP-2 reactivity. Anti-MDA5 antibodies were seen in three adult DM patients, antibodies against SAE-1 were noted in three and anti- SAE-2 was identified in two DM patients. These results indicate that the novel MAA can aid in phenotyping patients, especially when testing negative for ASS and anti-SRP, antiMI2.

5.1.5 What does the higher prevalence of sIBM in Norway tell us?

In our current study, multiple acquisition routes were applied to identify all the sIBM cases in South-East Norway over a 10-year period. With this strategy, we estimated the point prevalence of sIBM in Norway at study end to 33/1.000 000 by the 1997 and 2011 ENMC criteria (35/ 1.000 000 total). This estimate is substantially higher than previous European estimates. [79, 153, 159]

The contingency of familial or hereditary cases being included as sIBM, due to the lacking knowledge, might be a possibility. Another potential cause of an overestimation could be the usage of the recent published 2011 ENMC criteria[147] which is not extensively validated to date. It could be debated that there might be an overestimation due to the 2011 criteria's larger focus on clinical, rather than pathological findings.

Atypical PM or other rare neurological myopathies are other differential diagnosis which might have led to a overestimation, especially since the mean age at diagnosis in our PM cohort is higher than seen in many other studies.[180] But this notion should have been overcome by the 10 year follow-up of clinical picture and the notion that we discussed each case on a one to one basis in collaboration between neuropathologists and rheumatologists. Approximately 1/5th to 1/6th (15-20) patients did not initially fulfil the criteria, due to either 1) clinically lacking of distal weakness, especially finger flexor weakness, and these features became apparent over time. 2) The histopathology was initially not compatible with sIBM, but on re-biopsy the findings became apparent.

Another fact that undermines this is that 98% of patients classified with sIBM exhibited rimmed vacuoles in muscle biopsies, which is in contrast to other studies which exhibit a significantly lower percentage of patients to have rimmed vacuoles on muscle biopsy. This

fact might even lead us to believe that the prevalence of IBM in Norway is even greater than we have estimated?

Another suggestion for the much higher prevalence of sIBM in the Norwegian population may be genetic; a strong genetic influence by the MHC class II region has been reported in several inflammatory rheumatic disorders, however in many studies with different results. This is possible because of the actual differences in prevalence between distinct ethnic groups. Previous studies have shown that the HLA DRB1*03 allele is common in Scandinavia, but extremely rare in Japanese.[185] The exact population frequencies of Class II MHC alleles, HLA DRB1* 0301 in Norway, calculated from healthy controls in the bone-marrow registry is 13.1%, the same figure was recently seen in this study from Norway. [186]

5.1.6 Has mortality changed over the last decades?

Before the era of corticosteroids and anti-inflammatory therapy, the prognosis was detrimental and survival of IIM was very low.[119, 187] In mortality studies from the 70ties, the outcome of IIM remained poor [91] with a five year survival rate lower than 50%.[4, 92-95] The more recent studies show mortality ratio in DM/PM patients remain threefold higher compared with the general population, with cancer, infection, lung and cardiac complications being the most common causes of deaths.[91]

Later work has confirmed this, but shown large variation in mortality rates, probably due to differences in patient selection, classification and loss to follow-up. [91]

Compared to the Norwegian background population, our cohort of 326 unselected IIM patients had decreased survival. Our study finds that the 10 year survival of 55% and 60% in DM and PM respectively, are no higher than previously observed in single-centre cohorts, [91, 97, 104]. The 10 year survival in sIBM was even lower (42%) in our cohort, but the low concurring survival in the matched controls (57%) showed that this was an effect of age. The age effect was also apparent in the risk factor analyses where mean age at diagnosis stood out as an important determinant of mortality across all the IIM cohorts

Hazard ratios were increased in all IIM subsets for cancer, highest in the DM, as seen in previous studies. [91, 104, 188, 189]. Reduced pulmonary function, expressed by FVC <70% and DLCO <60% were associated with increased mortality. These data appear in line with a study on 107 PM/DM patients where reduced FVC and DLCO were associated with mortality.[12]

Several previous studies have reported decreased survival in PM/DM patients with MAA [91, 99, 190-193]. Surprisingly, in our cohort MAA did not increase the Hazard ratio in any of the IIM subgroups. We speculate that this may be an effect of differential patient selection. Our

PM/DM cases were unselected, while the previous studies were from specialized centres that possibly selects for PM/DM patients with more severe disease and higher frequency of MAA-related organ complications like ILD and PH. Another possibility is that the recent availability of more efficient treatment has improved the relative survival of MAA positive patient subsets.

The major causes of death in our cohort PM/DM were cancer, infections and respiratory failure due to ILD and/or secondary PH, as reported by others.[23, 90, 91, 188] Interestingly, in sIBM it appeared that the major cause of death was a potentially preventable complication (aspiration secondary to oesophagus dysmotility). In conclusion the mortality of PM/DM remains high in Norway and some of the disease-related deaths in sIBM are potentially preventable.

5.1.7 How do we follow our IIM patients with increased risk of mortality and clinical implications?

Discussion on standards of care should always be a priority and an aim for international collaboration. To date the standards of care differ even amongst specialists. Therefore the aim should be to have international agreed consensus of “best practice” which can dramatically improve patient’s quality of life and in some cases increase survival. The international best practice guidelines should also encompass same diagnostic criteria sets, investigative and follow-up practice and same level of care.

In sIBM patients the aims could be to

- 1) Reduce diagnostic delay by awareness, education and standard diagnostic criteria utilized by doctors and allied health care personnel.
- 2) To investigate the possibility of dysphagia by radiological imaging and awareness. And to treat nutritional impairment and refer to Ear Nose Throat (ENT) specialists where surgical options are a possibility.
- 3) A treatment trial consisting of at least a short-term corticosteroids therapy and Methotrexate could possibly be standard care, especially in patients with other rheumatic inflammatory disorders.
- 4) Supportive management, orthotics, adaptive devices and exercise with physiotherapists could be sought.
- 5) Clinical trials of new potential beneficial treatments and international collaboration.

In PM/DM patients:

- 1) Focus should also be on awareness and education of health professionals and doctors and international collaboration for the usage of same diagnostic criteria and same level of care.
- 2) Focus initially should be on cancer screening, especially of DM patients. All patients, especially MAA positive, could be investigated at debut with;
 - a) HRCT of the lungs to exclude ILD and pulmonary complications
 - b) Pulmonary function tests (PFT)
 - c) Echocardiography to monitor and exclude the development of Pulmonary Hypertension.
 - d) In addition to the diagnostic investigations; blood samples for muscle enzymes, ESR, autoantibodies and MAA. EMG/neurography, radiological studies of the oesophagus, MRI of thigh muscles and muscle biopsy.

The patients at risk could possibly annually be followed by serial HRCT of the lungs, PFTs and Echocardiography.

- 3) Patients would possibly benefit from receiving tailored treatment according to phenotypes, internationally standardized.
- 4) A focus of treatment and prophylactic antibiotics should be given to severely immunosuppressed patients, especially those with organ-damage, to reduce infection-associated mortality.

- 5) The follow-up during the first years of diagnosis should be most extensive, due to the fact that most disease-related deaths occur during the first years of diagnosis.

5.2 Future perspectives:

The aim of this large epidemiological study was to map the prevalence, clinical characteristics and cancer and mortality of IIM in South-east Norway. With ambition to ultimately obtain better knowledge of the disorders that encompasses IIM and their outcomes. We do, however, have concrete plans and wishes for further studies, as there is yet unpublished clinical data and important aspects to elaborate. We especially want to further investigate the recent trial on novel MAA undertaken on approximately 152 of our patients. (Sanner et.al) The results from this study indicate that the new MAA may aid clinical decision making in adult IIM, especially in patients negative for anti-synthetase and anti-SRP antibodies. We wish to include the entire IIM cohort, in order to test this hypothesis further. In addition, we also plan and aim to undertake further genetic and molecular studies and we hope to extend the cohort nationally to include the whole of Norway. We also wish and hope we are able to contribute internationally with clinical data to give more grounds for larger research, through MYONET and other collaborative efforts. We do believe that this is the way forward to increase the level of care of IIM patients in Norway.

6. Reference list

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Appendix I:

Selected abbreviations

ANA anti-nuclear antibody

ANM autoimmune necrotizing myopathy

Anti-HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A reductase

Anti-SSA: Sjögren's syndrome A antibody

Anti-SRP: Anti-Signal Recognition Particle

ASS Anti-synthetase syndrome

Aza: Azathioprine

CI: Confidence Interval

CK: Creatine Kinase enzyme

COP Cryptogenic organizing pneumonia

CTD: Connective tissue disease

CYC: Cyclophosphamide

DLCO: Diffusion Capacity of carbon monoxide

DM Dermatomyositis

EMG: Electromyography

ENMC: European Neuro-Muscular Centre

ESR Erythrocyte Sediment Rate

FEV1 Forced expired volume in one second

FVC forced vital capacity

GC Glucocorticosteroids

HLA Human leucocyte antigen

HRCT thorax high resolution computed tomography

ICD10 International Classification of Diseases 10th version

IG Immunoglobulin

IIM idiopathic inflammatory myopathy

IMMCP: International Myositis Classification Criteria Project

ILD Interstitial lung disease

IPF Idiopathic Pulmonary fibrosis

MHC major histocompatibility complex

MAA myositis associated autoantibodies

MMF Mycophenolate mofetil

MMT manual muscle test

MTX Methotrexate

MRC scale: Medical Research Council scale

MRI Magnetic resonance imaging

MSA myositis specific antibodies

NOSVAR Norwegian Systemic Connective Tissue and Vasculitis Registry

NSIP Non-specific interstitial pneumonia

PH Pulmonary hypertension

PM Polymyositis

pSS primary Sjögren Syndrome

RA rheumatoid arthritis

REK Regional Committee for Research Ethics

RTX Rituximab

SD Standard Deviation

sIBM: Sporadic inclusion body myositis

SLE Systemic lupus erythematosus

SMR: Standard mortality rate

SIR: Standard incidence rate

SNOMED: Systematic Nomenclature of Medicine code system

UIO University of Oslo

UIP usual interstitial pneumonia

Errata

Paragraph 1.1.2, page 11; changed from;

while, the Gottron`s papules are typically described as symmetrical papules over the extensor (dorsal) aspects of the metatarsophalangeal (MCP) and interphalangeal (IP) joints, The Gottrons sign is the same rash as above when present on the extensor surfaces of other joints

To:

while the Gottron`s papules are typically described as erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. This manifestation may occur over the finger joints, elbows, knees, malleoli and toes. The Gottrons sign is erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable.

Paragraph 1.1.6, page 16 to18.

Changed Myositis Associated Autoantibodies (MAA) to Myositis Specific Autoantibodies (MSA) throughout this paragraph.