From Department of Medicine, Solna
Karolinska Institutet, Stockholm, Sweden

RISK FACTORS AND OUTCOMES IN INFLAMMATORY MYOPATHIES

Valérie Leclair

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Risk factors and outcomes in inflammatory myopathies
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By

Valérie Leclair

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Principal Supervisor:
Associate Professor Marie Holmqvist
Karolinska Institutet
Department of Medicine, Solna
Division of Clinical Rheumatology

Co-supervisor(s):
Professor Ingrid Lundberg
Karolinska Institutet
Department of Medicine, Solna
Division of Rheumatology

Associate Professor Marie Hudson
McGill University
Department of Medicine
Division of Rheumatology

Opponent:
Professor Pedro Machado
University College London
Department of Medicine
Division of Rheumatology

Examination Board:
Professor Katja Fall
Örebro Universitet
Department of Medicine
Division of Clinical Epidemiology

Associate Professor Maria Altman
Karolinska Institutet
Department of Medicine, Solna
Division of Pediatric Rheumatology

Associate Professor Andreas Jönsen
Lund University
Department of Medicine
Division of Rheumatology

Abstract

Idiopathic inflammatory myopathies (IIM) are complex autoimmune diseases associated with high morbidity and mortality. Although knowledge about the pathogenic mechanisms underlying IIM is improving, limited data are available to inform clinical decision-making contributing to overall poor clinical outcomes in that population. The different projects in this thesis aimed to generate knowledge to help improve clinical outcomes in IIM and covered a wide range of topics related to outcome research namely risk factors, drug effectiveness, morbidity, mortality, and healthcare costs.

In **study I**, genetic predisposition to autoantibody development in IIM was studied using a large international cross-sectional study. Based on an unsupervised cluster analysis, eight autoantibody-defined IIM subgroups were identified, and associated with distinct HLA class II and I, supporting the incorporation of autoantibody profiles in future IIM classification projects.

In **study II**, based on a single center experience, significant improvement in physical function was found in anti-aminoacyl tRNA synthetase (ARS) positive patients but not in anti-ARS negative patients after exposure to one cycle of rituximab. Moreover, 78% of anti-ARS positive and 50% of anti-ARS negative patients achieved moderate/major ACR/EULAR improvement, supporting the effectiveness of rituximab in IIM.

In **study III**, using Swedish administrative databases, a 2.4-fold higher risk of acute coronary syndrome (ACS) was found in patients with IIM compared to the general population. When accounting for the competing risk of death, the cumulative incidence of ACS at 5 years was estimated at 7% in IIM compared to 3% in the general population, confirming the substantial cardiovascular burden in IIM.

In **study IV**, a modification effect of cancer on the association between dysphagia in early disease and mortality was demonstrated using an international IIM cohort. While dysphagia exposure in the absence of cancer was not associated with higher mortality risk, exposure to dysphagia in the presence of cancer was associated with a 5-fold higher mortality risk when compared to patients with IIM unexposed to dysphagia and cancer. This finding highlights the importance of stratification on cancer status when studying mortality in IIM.

In **study V**, annual healthcare costs in IIM were estimated using Swedish administrative databases and found to be 3 to 5-fold higher than the general population in the 5-year period following diagnosis. In addition to providing the first Swedish estimates of IIM healthcare costs, this study emphasized the significant contribution of indirect costs that accounted for 40 to 60% of the overall annual costs over the five-year period after IIM diagnosis.

Thus, the results generated by these studies demonstrate novel HLA associations with autoantibody-defined subgroups in IIM while supporting the effectiveness of B-cell depletion, confirming the increased cardiovascular risk, and shedding light on the relationship between dysphagia and mortality in IIM. These results, along with the comprehensive estimates of IIM healthcare costs, are valuable to define the orientation of future studies that will help bridge the therapeutic gap, reduce the cardiovascular burden, and improve cancer-associated management in IIM.

List of scientific papers

I. Leclair V, Galindo-Feria AS, Rothwell S, Krystufkova O, Sarrafzadeh Zargar S, Mann H, Diederichsen LP, Andersson H, Klein M, Tansley S, The DISSECT Consortium, McHugh N, Lamb J, Vencovsky J, Chinoy H, Holmqvist M, Bianchi M, Lindblad-Toh K, Padyukov L, Lundberg IE, Diaz-Gallo LM. **HLA associations with autoantibody-defined subgroups in idiopathic inflammatory myopathies.**
Manuscript.

II. Leclair V, Galindo-Feria AS, Dastmalchi M, Holmqvist M, Lundberg IE. **Efficacy and safety of rituximab in anti-synthetase positive and negative patients – A register-based study.** *Rheumatology (Oxford)* 2019;58(7):1214-1220. doi: 10.1093/rheumatology/key450.

III. Leclair V, Svensson J, Lundberg IE, Holmqvist M. **Acute coronary syndrome in idiopathic inflammatory myopathies: a population-based study**. *Journal of Rheumatology* 2019;46(11):1509-1514. doi: 0.3899/jrheum.181248.

IV. Leclair V, Notarnicola A, Krystufkova O, Mann H, Andersson H, Diederichsen L, Vencovsky J, Lundberg IE, Holmqvist M, Steele R, Hudson M. **Effect modification of cancer on the association between dysphagia and mortality in early idiopathic inflammatory myopathies**. Manuscript.

V. Leclair V, Moshtaghi-Svensson J, Regardt M, Hudson M, Lundberg IE, Holmqvist M. **Distribution and trajectory of direct and indirect costs of idiopathic inflammatory myopathies**. *Seminars in Arthritis and Rheumatology* 2021;51(5):983-988. doi: 10.1016/j.semarthrit.2021.07.016.

Scientific papers not included in the thesis

I. Leclair V, Lundberg IE. **New Myositis Classification Criteria - What We Have Learned Since Bohan and Peter.** *Curr Rheumatol Rep* 2018;20(4):18.

II. Leclair V, Landon-Cardinal O, Aggarwal R, Bansback N, Campbell C, Feldman BM, Jarry M, McNamara S, White B, Hudson M; CIMS investigators. **Proceedings of the 2019 Canadian Inflammatory Myopathy Study Symposium: Clinical Trial Readiness in Myositis**. *J Rheumatol* 2020;47(10):1584-1586.

III. Leclair V, Notarnicola A, Vencovsky J, Lundberg IE. **Polymyositis: does it really exist as a distinct clinical subset?** *Curr Opin Rheumatol* 2021;33(6):537-543.

IV. Leclair V, Tsui H, Hudson M. **Pain in autoimmune inflammatory myopathies – a scoping review.** *RMD Open.* 2023 Jan;9(1):e002591.

V. Leclair V, Bernatsky S, Hudson M. In: Christopher-Stine L, Lundberg I, editors. The Myositis Handbook: An Inclusive Guide to the Inflammatory Myopathies – **Chapter 2: Epidemiology of Adult Idiopathic Inflammatory Myopathy**: Jaypee Medical Publishers; 2023.
In press.

Contents

List of abbreviations

ACR	American College of Rheumatology
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCA	Antineutrophil cytoplasmic antibody
ARS	Aminoacyl tRNA synthetases
AST	Aspartate aminotransferase
ASyS	Anti-synthetase syndrome
CI	Confidence interval
CIMS	Canadian Inflammatory Myopathy Study
CK	Creatine kinase
cN1A	Cytosolic 5′-nucleotidase 1A
CS	Corticosteroids
CSM	Core set measures
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte Antigen-4
DM	Dermatomyositis
DMARD	Disease-modifying anti-rheumatic drugs
DOI	Definition of improvement
Fc	Fragment crystallizable
eIF3	Eukaryotic initiation factor 3
EJ	Glycyl t-RNA synthetase
ELISA	Enzyme-linked immunosorbent assay
ENMC	European Neuromuscular Center
EULAR	European Alliance of Associations for Rheumatology
FHL1	Four-and-a-Half-LIM domain 1
Ha	Tyrosyl t-RNA synthetase
HAQ	Health Assessment Questionnaire
HLA	Human leukocyte antigen
HMGCR	3-hydroxy-3-methylglutaryl coenzyme A reductase

HR	Hazard ratio
HRQoL	Health-related quality of life
IBM	Inclusion body myositis
IFNγ	Interferon γ
IIM	Idiopathic inflammatory myopathy
IL	Interleukin
ILD	Interstitial lung disease
IMACS	International Myositis Assessment and Clinical Studies
IMNM	Immune-mediated necrotizing myopathy
IPW	Inverse probability weighting
IVIg	Intravenous immunoglobulins
JDM	Juvenile dermatomyositis
Jo1	Histidyl t-RNA synthetase
KS	Asparaginyl t-RNA synthetase
LDH	Lactate dehydrogenase
MAA	Myositis-associated antibodies
MAC	Membrane attack complex
MDAAT	Myositis Disease Activity Assessment Tool
MDA5	Melanoma differentiation associated protein 5
MHC	Major histocompatibility complex
MITAX	Myositis Intention to Treat Index
Mi2	Nucleosome remodelling deacetylase complex
MMT	Manual muscle testing
MSA	Myositis-specific antibodies
MxA	Myxovirus resistant protein
MYOACT	Myositis disease activity assessment visual analog scales
NF-kB	Nuclear factor-kappa B
NSTEMI	Non ST-elevation myocardial infarction
NXP2	Antinuclear matrix protein 2
OJ	Isoleucyl t-RNA synthetase

OM	Overlap myositis
OR	Odds ratio
PFT	Pulmonary function testing
PGA	Physician global assessment
PL7	Threonyl t-RNA synthetase
PL12	Alanyl t-RNA synthetase
PM	Polymyositis
PM/Scl .	Exosome protein complex
RIM	Rituximab in Myositis
Ro52	TRIM21 located in cytoplasm and nucleus
Ro60	Small cytoplasmic ribonucleoprotein complexes
SAE	Small ubiquitin-like modifier activating enzyme
SF-36	36-Item Short-Form Survey
SMN	Survival of motoneuron
SRP	Signal recognition particle
STEMI	ST-elevation myocardial infarction
Th	T helper
TIF1γ	Transcriptional intermediary factor 1γ
TNF	Tumor necrosis factor
U1-snRNP	U1-Small nuclear ribonucleoprotein
UK	United Kingdom
US	United States
VAS	Visual analog scale
VFSS	Videofluoroscopy swallowing study
Zo	Phenylalanyl t-RNA synthetase

1 Introduction

Idiopathic inflammatory myopathies (IIM) consist of a heterogenous group of multisystemic autoimmune diseases that predominantly affect the muscles but can also involve other organs such as skin, lungs, or gastrointestinal tract. Decades of research and careful clinical assessments have resulted in the description of distinct clinical phenotypes within the IIM spectrum. However, now that identification and classification have improved, different questions are arising. Is there a classification scheme that delineates more homogenous subgroups and better reflects disease mechanisms? What treatments are more effective for which subgroups of IIM patients? What short-term and long-term complications are to be expected, and how can we mitigate these? In other words, the focus is shifting towards improving clinical outcomes in IIM.

Outcome is a broad term referring to the result or effect of an action[1]. At first glance, the term *outcome research* could then apply to most branches of research. In reality, this research field emerged in the 1960's and encompasses specific topics[2]. The goal of outcome research is to improve patient care and inform physicians as well as policy makers about the value of medical interventions. It includes different areas of research such as decision making, drug effectiveness, morbidity, mortality, and costs (**Figure 1**).

With many areas of uncertainty and unmet needs, there is a pressing need for outcome research in the field of IIM. The projects included in this thesis leveraged multiple existing data sources to generate novel findings and broaden our understanding of the genetic predisposition to the disease, while providing insights to improve clinical outcomes in IIM.

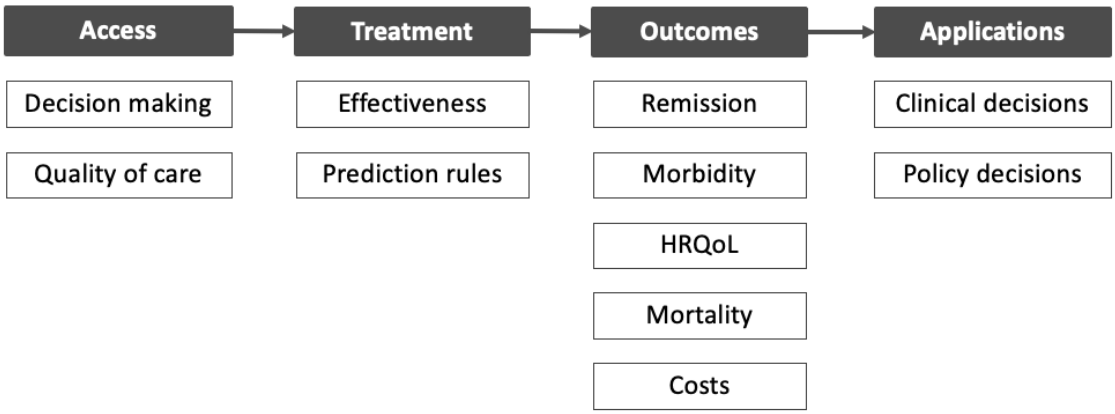

Figure 1 | Different outcome research topics
HRQoL; health-related quality of life

2 Literature review

2.1 Incidence and prevalence

The epidemiology of IIM varies widely depending on classification criteria and methodology used. In general, IIM incidence and prevalence are increasing with time, likely due to improved disease detection and survival[3]. In 2012, the incidence of IIM in Sweden was estimated at 11/million/year (95%CI 10-12) and the prevalence at 14/100 000 (95%CI 13-15)[4]. In Canada, the prevalence of IIM in 2003 based on similar case definitions was 15.6/100 000[5]. **Figure 2** depicts the incidence and prevalence published in the literature and clearly illustrates the large geographical gaps in knowledge[6].

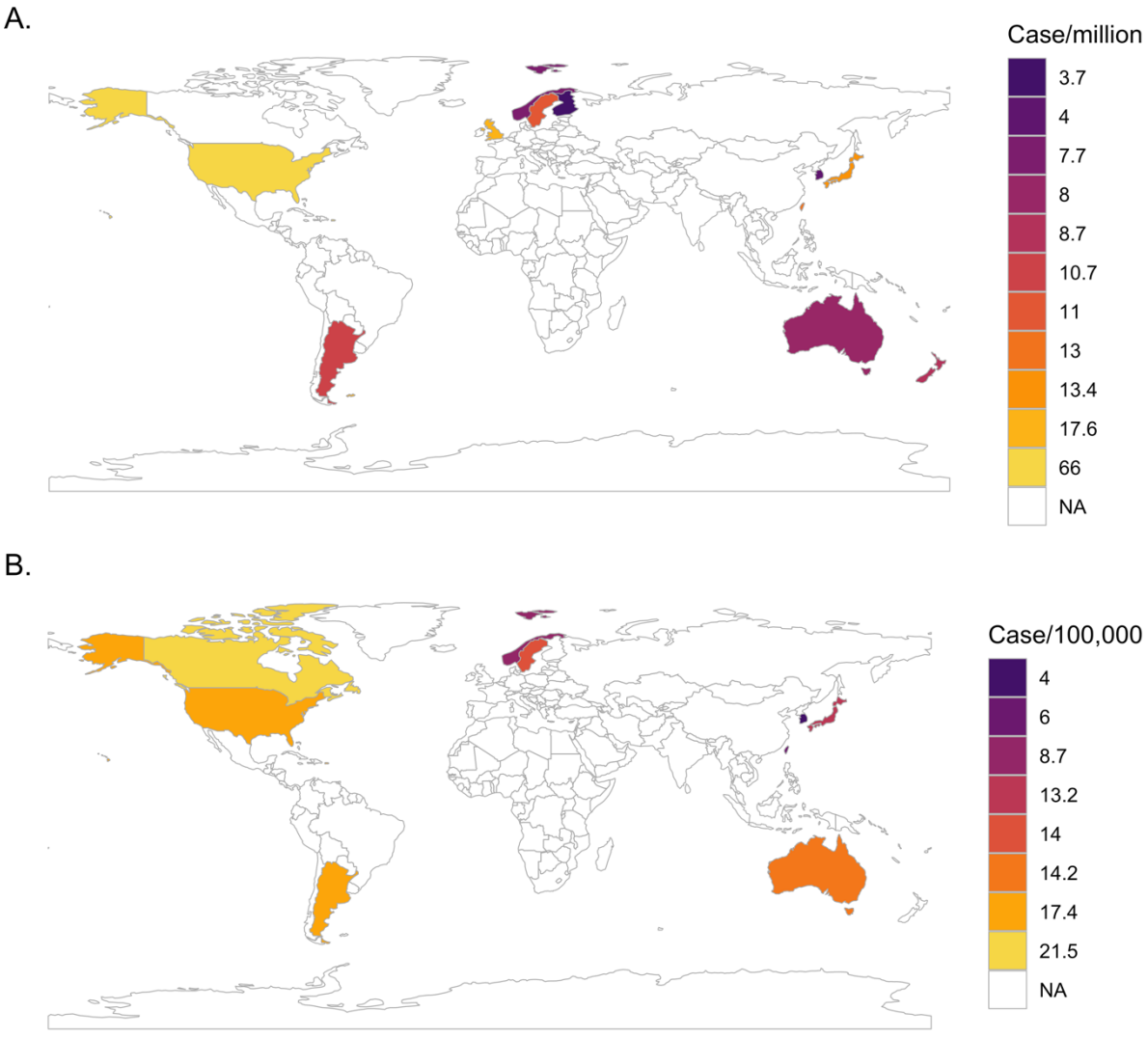

Figure 2 | Incidence and prevalence of adult IIM[6]
Panel A. Incidence per million of persons at risk per year in the United States of America (USA), Argentina, United Kingdom (UK), Norway, Finland, Sweden, Taiwan, Japan, Korea, Australia, and New Zealand. Panel B. Prevalence per 100 000 persons in the USA, Canada, Argentina, Norway, Sweden, Taiwan, Japan, Korea, and Australia.
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2.2 Clinical presentation

Muscle involvement

Muscle weakness is usually present in IIM, but in certain cases it can be subclinical (hypomyopathic) or absent (amyopathic). The classical pattern of weakness is symmetrical with involvement of the proximal muscles of the upper and lower extremities as well as the neck flexors. Distal weakness should not, however, be overlooked as it can be found in all subsets and is associated with important functional impact[7,8]. In inclusion body myositis (IBM, **section 2.4**), muscle involvement is asymmetric and affects predominantly the orbicularis oculi, biceps, quadriceps femoris, long finger flexors, and ankle dorsiflexors[9].

Different modalities can be used to detect muscle involvement notably serum muscle enzymes tests, electromyography, magnetic resonance imaging and muscle biopsies. On electromyography, the presence of increased insertional irritability and spontaneous activity with short-duration low amplitude polyphasic motor unit action potentials are suggestive of a myopathic process[10]. Muscle magnetic resonance imaging can show muscle and perifascial edema on T2-weighted short tau inversion recovery images and can be useful to detect subclinical muscle involvement, guide muscle biopsy or monitor disease activity[11,12]. Finally, muscle biopsies are very useful to document the presence of inflammation and autoimmune features while excluding potential mimickers of IIM such as muscular dystrophies or metabolic myopathies[13]. Certain histopathological features are also highly suggestive of specific subsets of IIM and can help with classification[10,14].

Extramuscular involvement (Figure 3)

Skin is frequently involved in IIM with heliotrope rashes, Gottron's papules (i.e., violaceous papules over the fingers) and Gottron's signs (i.e., macular violaceous erythema over the extensor surfaces of fingers, elbows, knees, and malleoli) being cardinal features of dermatomyositis (DM, **section 2.4**). Other skin manifestations such as alopecia, periungual erythema, mechanic's hands, violaceous erythema of the scalp, face, neck, thorax, extensors surfaces, lateral thighs and malleoli are also found[15]. Severe lesions such as erythroderma, vesiculobullous eruptions, ulceration, panniculitis, and calcinosis are less frequent[16]. Raynaud phenomenon is reported in about a third of patients[16,17].

Joint involvement in IIM is heterogeneous and can present in every disease subset at any time point during the disease course, sometime being the sole presenting symptom[18,19]. Non-erosive polyarthritis, and less frequently oligoarthritis and monoarthritis, have been described in IIM with a predominance for upper extremity involvement[19–21].

Depending on methodology used and population included, interstitial lung disease (ILD) is reported in 17 to 65% of patients[22]. On high-resolution computerized tomography of the chest, the most frequent ILD patterns are organizing pneumonia and non-specific

interstitial pneumonia. More rarely, usual interstitial pneumonia can be present[23]. Pulmonary function testing in the presence of ILD often reveals a restrictive pattern and diminished diffusing capacity of the lung for carbon monoxide. Of note, respiratory muscle weakness can also cause a restrictive pattern and pulmonary arterial hypertension can impair carbon monoxide exchange which might complicate the interpretation of pulmonary function tests. Bronchoalveolar lavage cell count can help support a diagnosis of ILD and is an important procedure to rule-out infections[24]. Lung biopsies are performed in rare, atypical cases and show similar features as idiopathic ILD. Pulmonary hypertension can complicate severe ILD, while pulmonary arterial hypertension occurs less commonly[25,26]. Given the technical challenge of diagnosing respiratory muscle weakness in clinical practice, the exact prevalence of this severe manifestation is unknown and most likely underestimated[27].

Arrhythmias such as atrial fibrillation and supraventricular tachyarrhythmias are more prevalent in individuals with IIM than in the general population with estimates ranging from 25 to 45%[28,29]. Myocarditis is rare (prevalence ~5%) but can be fatal[30]. Post-mortem histopathological studies have shown similar findings in the myocardium and skeletal muscles of patients with IIM, with myocardial endomysial and perivascular inflammatory infiltrates[31]. While the gold standard for the diagnosis of myocarditis remains endomyocardial biopsy, in practice, clinicians most often rely on non-invasive methods such as high sensitivity cardiac troponin levels and cardiac magnetic resonance imaging for myocarditis detection[32-34].

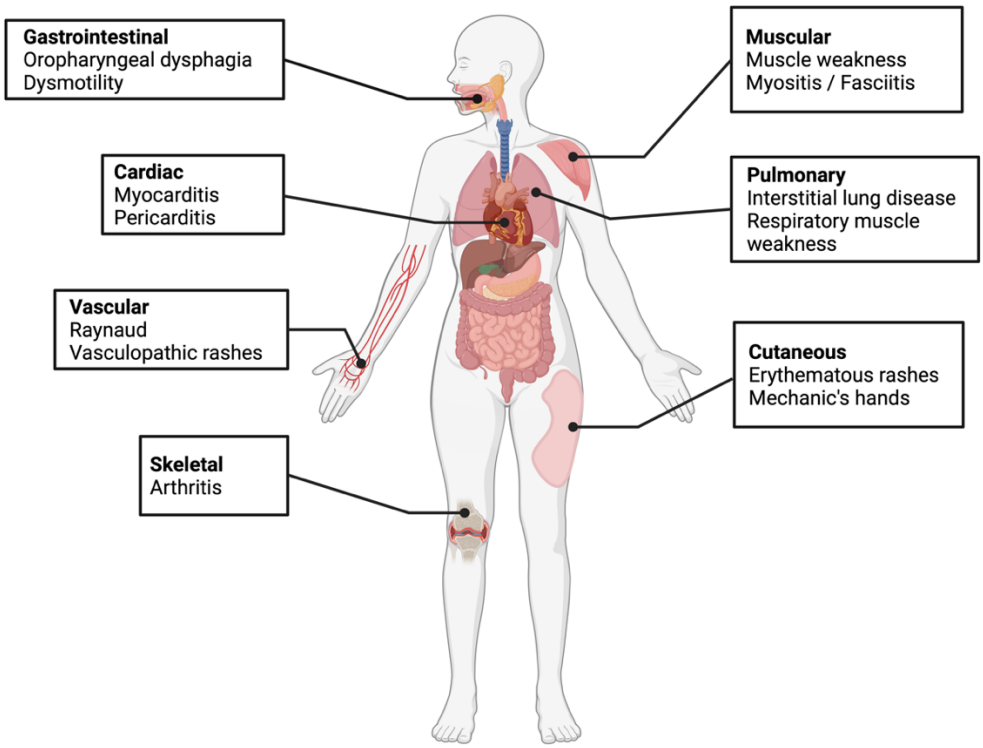

Figure 3 | Different organ involvement in IIM
Created with BioRender.

Based on focus groups, dysphagia, dyspepsia, constipation, diarrhea, and incontinence are major concerns for patients with IIM[35]. This large range of gastrointestinal symptoms is not reflected in the literature and lower gastrointestinal tract involvement in adult IIM was never systematically studied and consists mainly of case reports/series[36]. A recent meta-analysis estimated the pooled prevalence of dysphagia in IIM at 36%[37]. Reduced pharyngeal contractility, cricopharyngeal dysfunction and reduced laryngeal elevation are documented on videofluoroscopy, flexible endoscopy, and manometry in IIM and are thought to result from inflammation of the skeletal muscles of the oropharynx and upper third of the esophagus[36].

Although this mechanism seems likely, endomysial inflammatory infiltrates in cricopharyngeal muscles have rarely been documented as is the case for oropharyngeal muscle edema on magnetic resonance imaging[38-41]. The lower part of the esophagus consists of smooth muscle and the mechanisms underlying lower esophageal dysfunction (i.e., reduced peristalsis, delayed transit, reduced lower esophageal sphincter pressure) in IIM are unclear[42]. Based on high-resolution manometry, dysmotility is nonetheless a frequent finding in this population with poor correlation with subjective assessment[43].

2.3 Autoantibodies

Since the description in 1976 of an autoantibody targeting the nucleosome remodeling deacetylase complex (Mi2) in DM, numerous myositis-specific antibodies (MSA) have been described including anti-aminoacyl tRNA synthetases (ARS), -melanoma differentiation antigen 5 (MDA5), -antinuclear matrix protein 2 (NXP2), -small ubiquitin-like modifier activating enzyme (SAE), -transcriptional intermediary factor 1γ (TIF1γ), -signal recognition particle (SRP), -3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) and -eukaryotic initiation factor 3 (eIF3)[44-46]. Anti-ARS, including autoantibodies against histidyl (Jo1), threonyl (PL7), alanyl (PL12), glycyl (EJ), isoleucyl (OJ), tyrosyl, (Ha), asparaginyl (KS) and phenylalanyl (Zo), are the most prevalent MSAs, being found in about 20% of individuals with IIM[47].

Autoantibodies found in IIM but not specific to the condition are labelled myositis-associated antibodies (MAA). The most frequent MAA is the anti-tripartite motif-containing protein 21 (TRIM21)/Ro52, followed by anti-Ro60, -U1-snRNP, -PM/Scl and -Ku. In 2013, the anti-cytosolic 5'-nucleotidase 1A (cN1A) was described in IBM[48,49]. Although this autoantibody is relatively specific for the condition, it was also found in other subsets of IIM and rheumatic conditions such as systemic lupus erythematosus, systemic sclerosis and Sjögren's syndrome[50].

Rarer autoantibodies, including autoantibodies against the survival of motor neuron (SMN) complex and RUVBL1/2 complex, have also been described in a few cases of systemic sclerosis patients with skeletal muscle involvement[51-53]. Finally, autoantibodies against

four-and-a-half-LIM domain 1 (FHL1) were recently described in IIM in the presence of severe muscle involvement, frequent dysphagia, and vasculitis, although these clinical associations were not replicated in an independent cohort[54,55].

Table 1 summarizes the prevalence of MSA/MAA. Of note, those estimates vary significantly in the literature depending on methods used for autoantibody detection, and enrichment of cohorts with specific IIM subsets. Moreover, some autoantibody levels are known to vary with disease activity and time points at autoantibody detection may affect frequency in prevalent cohorts[56,57].

Table 1 | Autoantibodies and their frequency in IIM cohorts[47,48,51-55,58-67]

Autoantibodies	Antigenic target	Frequency
MSA		
Jo1	Histidyl t-RNA synthetase	20%
PL7	Threonyl t-RNA synthetase	<5%
PL12	Alanyl t-RNA synthetase	<5%
EJ	Glycyl t-RNA synthetase	<5%
OJ	Isoleucyl t-RNA synthetase	<5%
KS	Asparaginyl t-RNA synthetase	<5%
Ha	Tyrosyl t-RNA synthetase	<5%
Zo	Phenylalanyl t-RNA synthetase	<5%
MDA5	Melanoma differentiation associated gene 5	<5%
Mi2	Nucleosome remodelling deacetylase complex	5-10%
NXP2	Nuclear matrix protein 2	<5%%
SAE	Small ubiquitin-like modifier activating enzyme	<5%%
TIF1γ	Transcription intermediary factor 1γ	10%
SRP	Signal recognition particle	<5%
HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase	5%
eIF3	Eukaryotic initiation factor 3	<5%
MAA		
cN1A	Cytosolic 5′-nucleotidase 1A	20-40%
PM/Scl	Exosome protein complex	7%
U1-snRNP	Small nuclear ribonucleoprotein	10%
Ro52	TRIM21 located in cytoplasm and nucleus	25-50%
Ro60	Small cytoplasmic ribonucleoprotein complexes	20%
Ku	Ku complex	<5%
RUVBL1/2	RUVBL1/2 complex	<5%
SMN	Survival of motoneuron	<5%
FHL1	Four-and-a-Half-LIM domain 1	15-25%

2.4 Clinical phenotypes

Dermatomyositis (DM)

DM is generally defined by the presence of skin rashes typical for the condition (i.e., heliotrope rash, Gottron's papule, Gottron's sign). Several MSA are associated with DM and are characterized by some distinctive features (**Table 2**). In addition, specific muscle features on histopathology characterize this subset including perifascicular atrophy and evidence of myovasculopathy with perimysial perivascular inflammatory infiltrates, decreased capillary density and complement deposition in capillaries[68]. Of note, the presence of these histopathological findings can vary, and some DM patients have normal muscle biopsies. Tubuloreticular inclusions in endothelial cells on electron microscopy can be found but are not specific to the subset[69]. DM patients are at increased risk of cancer, an association that differs depending on autoantibody-defined subsets[70].

Table 2 | Distinctive features of autoantibody-defined DM subsets[14,71]

	Skin features	Muscle pathology	Dysphagia	Cancer
Anti-MDA5	Palmar papules Ulcerative lesions	No or focal inflammation Scattered/diffuse MxA staining	30%	+
Anti-Mi2	Typical	Perifascicular MxA staining Sarcolemmal MAC deposits	20%	+
Anti-NXP2	Calcinosis	Micro-infarction Perifascicular ALP staining	30%	++
Anti-SAE	Typical	Scattered or perifascicular MHC staining	60%	+
Anti-TIF1*γ*	Palmar papules Psoriasis-like lesions Hypopigmented telangiectatic patches	Punched-out vacuoles Perifascicular MHC staining	50%	+++

ALP, alkaline phosphatase; MAC, membrane attack complex; MHC, major histocompatibility complex; MxA, myxovirus resistant protein.

Immune-mediated necrotizing myopathy (IMNM)

IMNM is mainly characterized by muscle involvement with muscle histopathology showing predominantly necrotic fibers with sparse inflammatory infiltrates and possible sarcolemmal membrane attack complex (MAC) deposition[10]. Anti-HMGCR and -SRP autoantibodies are associated with this subset, but a proportion of IMNM patients are seronegative[72]. Anti-HMGCR autoantibodies are associated but not exclusive to individuals exposed to statins[73]. Although the IMNM phenotype is mostly characterized by skeletal muscle symptoms, anti-SRP positive patients can present with ILD and dysphagia[74]. IMNM histopathological features in seronegative patients should raise concerns for a paraneoplastic syndrome or a possible overlap with scleroderma[75,76].

Anti-synthetase syndrome

The anti-synthetase syndrome is often defined by positivity to an anti-ARS autoantibody in the presence of myositis and/or extramuscular features such as ILD, fever, arthritis, or mechanic's hand[77,78]. ILD can dominate the symptomatology and be the main presenting feature particularly with rarer anti-ARS autoantibodies such as anti-PL7, -PL12 and -EJ[79]. On muscle histopathology, anti-synthetase syndrome demonstrates perimysial inflammatory infiltrates as described in DM while perimysial fragmentation, perifascicular necrosis and MAC sarcolemmal positivity are striking distinctive features of the syndrome[68,80].

Overlap myositis

Overlap myositis is a heterogenous subset with varying definitions in the literature. Initially, Bohan and Peter defined overlap myositis as having DM or PM while meeting classification criteria for another connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis[81,82]. A more contemporary definition is based on the presence of overlap features (e.g., Raynaud phenomenon, arthritis, ILD, mechanic's hands) without the requirement to meet the full diagnostic / classification criteria for another connective tissue disease[83,84]. A limitation of this approach is that overlap features are highly prevalent in IIM creating a large and heterogenous subgroup that is often excluded from clinical trials and translational projects. This limits our understanding of the pathogenic mechanisms and clinical outcomes of overlap myositis.

Polymyositis (PM)

Based on earlier classification / diagnostic criteria, PM comprised patients with proximal muscle weakness, elevated muscle enzymes, myopathic electromyogram and endomysial inflammatory T-cell infiltrates surrounding and/or invading nonnecrotic muscle fibers on skeletal muscle histopathology without DM rashes[85]. Improved clinical assessments, autoantibody discovery and more detailed immunophenotyping of inflammatory infiltrates helped re-classify many cases previously labelled as PM as, among other things, anti-synthetase syndrome, IMNM and even DM without rash. PM now represents a very small portion of IIM[86].

Inclusion body myositis (IBM)

Although included in the IIM spectrum, IBM remains somewhat of an outlier. While other IIM generally occur between 40-70 years of age with a female predominance (2:1), IBM usually presents after the age of 60 with a male predominance (1.5:1)[3,87]. The muscle weakness is often asymmetric and preferentially involves finger flexors, knee extensors and ankle dorsiflexors, although proximal muscles can also be affected. The disease onset is insidious with a lack of response to immunosuppression. On muscle histopathology, there is endomysial lymphocytic CD8+ T-cell infiltrates surrounding and sometimes

invading muscle fibers. Mitochondrial abnormalities and cytomembranous whorls and tubulofilaments on ultrastructural analysis are frequent[88]. Although rimmed vacuoles on histopathology are often required for a pathological IBM diagnosis, about a third of patients do not display this feature, that is also not specific for the condition[89].

2.5 Classification

IIM classification is subject to debate amongst experts and this lack of consensus directly influences epidemiological and biological research in the field. For decades, symmetrical proximal muscle weakness associated with myopathic changes on electromyogram and/or histological features were central to IIM classification[81,82]. This approach has been challenged by the discovery of MSA, and the description of hypomyopathic or amyopathic subsets introduced in more contemporary classification schemes[10,83,90-94].

In 2004, the European Neuromuscular Center (ENMC) published the Muscle Study Group criteria[10]. These criteria combine clinical, laboratory and histopathological features to define six IIM subsets: DM, amyopathic DM, possible DM sine dermatitis, PM, non-specific myositis, and IMNM. The ENMC criteria rely heavily on histopathology with the rationale that this better reflects underlying pathogenic mechanisms. A purely pathological IIM classification was later introduced defining six pathological subsets: immune myopathy with perimysial pathology, myovasculopathy, immune polymyopathy, IIM with endomysial pathology, histiocytic inflammatory myopathy and inflammatory myopathy with vacuoles, aggregates, and mitochondrial pathology[68]. In 2013, the ENMC published IBM diagnostic criteria, often used as classification criteria, that categorized IBM as clinico-pathologically defined, clinically defined or probable IBM based on the presence of clinical, laboratory, and pathological features[95].

In 2017, the European Alliance of Associations for Rheumatology (EULAR) / American College of Rheumatology (ACR) published classification criteria for adult and juvenile IIM (**Table 3**)[94]. This classification divides adult and juvenile IIM based on age then separates DM from PM/IBM on the presence or absence of classic DM rashes (heliotrope rash, Gottron's papules or sign). Despite the robust methodology behind the 2017 EULAR/ACR classification criteria, they still include quite heterogeneous subsets and do not recognize anti-synthetase syndrome, overlap myositis, and IMNM as separate entities[85].

2.6 Risk factors

Environmental

DM patients have increased sensitivity to ultraviolet exposure, with rashes often involving sun-exposed areas[96-99]. Moreover, associations are reported between ultraviolet exposure intensity and increased DM prevalence[98-100]. Vitamin D deficiency is reported in IIM but given reverse causality issues, it remains uncertain if this is a risk factor for developing the condition or a consequence of reduced sun exposure[101].

Table 3 | 2017 EULAR/ACR classification criteria for adult and juvenile IIM[94]

Variables	Scores	
	No muscle biopsy	Muscle biopsy
Age of onset of first symptoms		
≥18 years and <40 years	1.3	1.5
≥40 years	2.1	2.2
Muscle weakness		
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors relatively weaker than neck extensors	1.9	1.6
In the lower extremities, proximal muscles are relatively weaker than distal muscle	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron's papules	2.1	2.7
Gottron's sign	3.3	3.7
Other clinical manifestations		
Dysphagia or oesophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-Jo1 positivity	3.9	3.8
Elevated muscle enzymes levels[§]	1.3	1.4
Muscle biopsy features		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

[§]Serum levels above the upper limit of normal for CK, AST, ALT or LDH.
Modified from Lundberg et al.[94] The authors recommend using a minimum of 55% probability (score of 5.5 without biopsies; 6.7 with biopsies) for classifying a case as a probable IIM. A definite IIM corresponds to a probability of at least 90% (score of ≥ 7.5 without biopsies; ≥ 8.7 with biopsies).

A large Danish population-based study reported an increased risk of developing IIM in individuals hospitalized for viral and bacterial infections[102]. A subsequent case-control study further suggested that infections of the respiratory and gastrointestinal tracts were risk factors for IIM development[103]. Interestingly, seasonality in disease onset was reported in anti-MDA5 positive patients in Japan, with higher incidence rates from October to March, a period corresponding to increased rates of respiratory infections (respiratory syncytial virus, influenza, and bacterial pneumonias)[104,105]. More recently, case reports have reported COVID-19 infections and vaccination as triggers for IIM development, but given their high risk of biases, large prospective studies will be required to infer causality[106,107].

Exposure to certain drugs and toxins are linked with IIM development notably statins that are strongly associated with anti-HMGCR positive IMNM[108,109]. Immune-checkpoint inhibitors, increasingly used to treat cancer, are also known to trigger inflammatory myopathies, but the clinical phenotype associated is distinct with frequent oculobulbar symptoms, myocarditis, and/or myasthenia gravis co-occurrence and infrequent MSA/MAA positivity[110,111]. Associations between tobacco smoking, ILD development and anti-Jo1 positivity are reported in IIM[112]. Moreover, some studies suggest that smoking exposure may confer a higher risk of developing anti-Jo1 in IIM individuals positive for *HLA-DRB1*03:01*[112,113].

Genetic

Genome-wide association studies in IIM demonstrates that the major histocompatibility complex (MHC) region plays an important role in the risk of developing the disease[114–116]. The MHC region on chromosome 6 contains the human leucocyte antigen (HLA) genes complex. HLA class II (HLA-DP, -DQ, -DR) and I (HLA-A, -B, -C) molecules present short peptides to T-cells, a key component of adaptive immunity. The strongest HLA associations in IIM are with *HLA-B*08:01* and *HLA-DRB1*03:01*, part of the 8.1 ancestral haplotype[117]. This highly conserved haplotype of multiple genes is frequent amongst Caucasians and is associated with the development of autoimmune diseases[118].

Previous studies have reported increased risks of developing certain IIM subsets and mutually exclusive MSA/MAA based on the presence of specific HLA molecules (**Table 4**) [44,116,119–127]. Amino acid configurations modify the structure of HLA molecules and influence T-cell antigenic presentation. Work by the MYOGEN consortium showed stronger associations between the presence of specific autoantibodies and amino acid positions compared to specific HLA alleles[126]. Genetic associations between HLA alleles and serological profiles including one or more MSA/MAAs have never been explored in IIM.

Table 4 | HLA alleles associated with autoantibodies in IIM[44,116,119–127]

	HLA class II		HLA class I
Autoantibodies	**HLA-DQ**	**HLA-DR**	**B**
Anti-Jo1		*DRB1*03:01*	*B*08:01*
Anti-Mi2	*DQA1*02, DQB1*02*	*DRB1*03:02, DRB1*07:01*	
Anti-MDA5		*DRB1*01:01, DRB1*04:05, DRB1*12:02*	
Anti-TIF1γ	*DQB1*02, DQA1*03*		
Anti-HMGCR		*DRB1*11:01*	
Anti-SRP	*DQA1*01:02, DQA1*01:04*	*DRB1*08:03*	*B*05:01*
Anti-cN1A		*DRB1*03:01*	
Anti-PM/Scl	*DQB1*02:01*	*DRB1*03:01*	
Anti-Ro		*DRB1*03:01, DRB1*08*	*B*08:01*
Anti-RNP		*DRB1*08*	

2.7 Pathogenic mechanisms

Innate immunity

Although IIM are characterized by the presence of autoantibodies and autoreactive lymphocytes, innate immunity seems to play an important role in initiating the immune response. Muscles are in a constant state of injury and regeneration due to physiological stress or infections. This can release damage-associated molecular patterns that may bind to Toll-like receptors on different immune cells and capillaries potentially triggering the secretion of pro-inflammatory cytokines and chemokines (e.g., type 1 interferon (IFN), TNFα)[128]. Cytokines and chemokines may then interact with their specific receptors on muscle structures activating downstream pathways while also causing direct structural damage leading to muscle fiber destruction, capillary loss, and muscle regeneration impairment[129]. In IIM, a central downstream pathway activated through this process is nuclear factor-kappa B (NF-kB) that modulates immune response and affects myogenesis[130]. Furthermore, immune and muscle cells can activate the inflammasome pathway with release of IL-1β, a pro-inflammatory cytokine[129].

Adaptive immunity

Through recognition of foreign peptide fragments presented by HLA molecules from antigen-presenting cells, T-cells can trigger autoantigen-specific immune responses. CD4+ and CD8+ T-cells play important roles in DM, PM and IBM[131]. Activated CD4+ T-cells in specific inflammatory milieu differentiate into T-helper (Th1, Th2, Th17) or T-regulatory cells[131]. Th1 and Th2 cells promote the generation of pro-inflammatory and anti-inflammatory macrophages, respectively. Th2 are further involved in B-cell maturation and differentiation in antibody-producing plasma cells. On the other hand, T-regulatory cells have an anti-inflammatory effect through inhibition of antigen-presenting cells and T-effector cells. CD4+ cells that are $CD28^{null}$ have been described in PM and DM muscles and have the particularity of differentiating into cytotoxic effector cells that are potent IFNγ and TNF producers[132].

B-cells have been described in PM, DM, and IBM and are essential to humoral immune response[129]. B-cells are antigen-presenting cells that can mature into plasma cells and produce autoantibodies. It remains unclear if the autoantibodies produced in IIM are pathogenic, but some evidence suggests that it could be the case with anti-Jo1, -MDA5, -HMGCR and -SRP[133]. Myeloid and plasmacytoid dendritic cells are major producers of type 1 IFN and have been found in the skin and muscle of DM patients[134,135]. The exact role of dendritic cells in IIM is uncertain, but they can activate CD4+ and CD8+ T-cells, while limiting inadequate autoreactive responses. Despite the significant advances in immunophenotyping of cells in muscle and skin of IIM patients, the exact pathogenic mechanisms leading to the development of the different subtypes remain unclear. This limits the identification of effective targeted therapies.

2.8 Treatment

Traditional disease-modifying anti-rheumatic drugs (DMARDs) and intravenous immunoglobulins (IVIg)

Contemporary IIM treatment often combines glucocorticoids and DMARDs such as azathioprine, methotrexate, calcineurin inhibitors, or mycophenolate mofetil with subsequent glucocorticoid tapering once an adequate clinical response is achieved[136]. Cyclophosphamide is frequently used for ILD treatment and for severe organ involvement such as myocarditis[137,138]. The ProDERM trial, a randomized placebo-controlled double-blind trial, confirmed the long-term efficacy and safety of IVIg in DM and led the US Food and Drug Administration to approve its use in this condition[139]. A small open label study in PM also showed benefit of IVIg[140]. Despite the paucity of evidence, IVIg are often used to treat dysphagia[141].

Biologic and targeted synthetic DMARDs

Rituximab was the first biologic to be studied in a large randomized controlled trial in refractory IIM, the Rituximab in Myositis (RIM) trial[142]. Rituximab is an anti-CD20 monoclonal antibody that targets mature naïve B-cells via different mechanisms (**Figure 4**). The trial used the International Myositis Assessment and Clinical Studies (IMACS) definition of improvement requiring a ≥20% improvement in three of any six IMACS core set measures, with no more than two worsening by ≥25%[143]. The IMACS core set measures include the physician and patient global activity assessment, extramuscular activity, manual muscle testing (MMT8), physical function measured by the Health Assessment

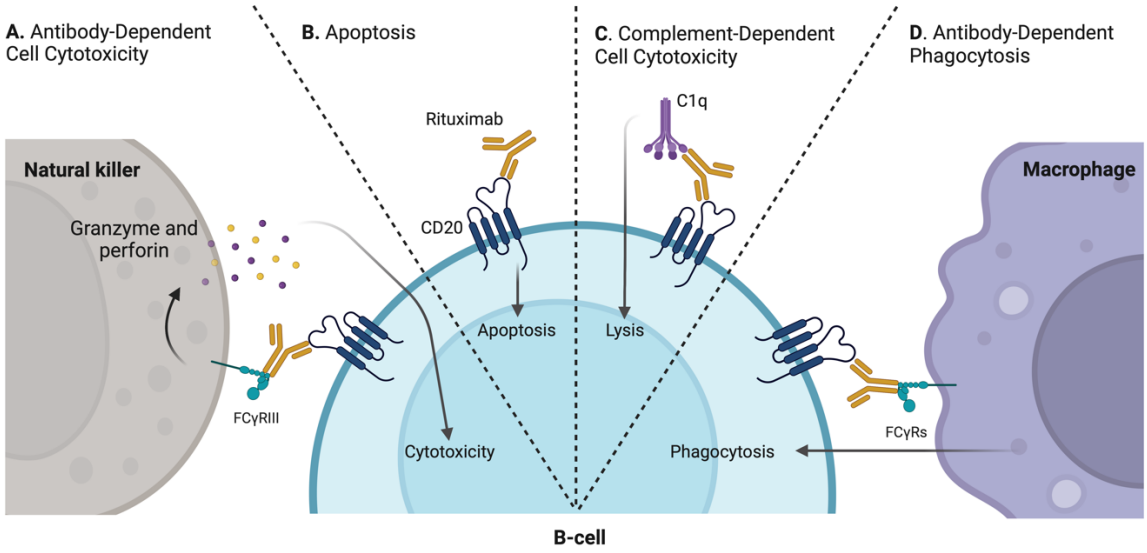

Figure 4 | Rituximab mechanisms of action[144]

Panel A. Effector cells bind to the anti-CD20 molecule through Fcγ receptors with subsequent release of effector molecules causing cell lysis. Panel B. Direct binding of rituximab on CD20 with direct toxicity and apoptosis. Panel C. C1q binding to the Fc portion of the anti-CD20 with activation of the complement cascade and cell lysis. Panel D. Recruitment of macrophages by Fcγ receptors binding and subsequent phagocytosis of antibody-coated cells. Created with BioRender

Questionnaire (HAQ) and muscle enzymes levels. In the definition of improvement used in RIM, the MMT8 could not be one of the worsening measures. Although no difference in time to achieve the definition of improvement between the late and early arms was found, 83% of the participants met the IMACS definition of improvement at 44 weeks[142]. Post-hoc analyses of the RIM trial showed that positivity for anti-ARS, and -Mi2 autoantibodies was associated with a favorable response to rituximab[145,146]. Similarly, several observational studies of rituximab in IIM reported clinical improvement in different disease subsets, particularly in the anti-synthetase syndrome (**Table 5**)[147–159]. However, these studies rarely compared response based on autoantibody status and are difficult to compare as they used variable clinical response definitions.

Abatacept, a fully human fusion protein of CTLA-4 and the fragment crystallizable (Fc) portion of human IgG1 that targets T-cell costimulation, was studied in the ARTEMIS trial[160]. This small phase 2b trial (n=19) randomized refractory IIM patients to an early or delayed (3 months) treatment arm. At 6 months, 42% of patients achieved the IMACS definition of improvement irrespectively of randomization arm. Furthermore, at 3 months the median ACR/EULAR total improvement score showed a significant difference between the early arm (treated) and delayed arm (untreated) in favor of the treated group. Case series and open-label pilot studies have reported impressive results with Janus kinase inhibition in refractory DM especially on skin involvement, with good safety profiles[161–164]. This treatment is increasingly used for anti-MDA5 positive patients with benefits noted in the lung and muscle compartments[165,166].

Although many options are available for IIM treatment, there is currently no data-driven guidelines to support specific sequences for treatment induction and maintenance. Clinicians are thus using "trial and error" approaches that lead to heterogenous practices likely contributing to delayed clinical remission and increased morbidity and mortality[167].

2.9 Comorbidities

Cancer

The cumulative incidence of cancer in IIM is higher than in the general population[168]. The results of a meta-analysis showed a pooled relative risk of cancer of 4.1 (95%CI 3.0-5.1) in overall IIM and 5.5 (95%CI 4.3-6.7) in DM compared to the general population[169]. A 2021 Swedish population-based study reported an increased risk of cancer peaking in the year prior to IIM diagnosis with an adjusted odds ratio (OR) of 4.4 (95%CI 3.2-6.1)[168]. DM subset, cutaneous ulcerations, anti-TIF1γ positivity, increasing age, male sex, and dysphagia were identified as clinical risk factors for cancer in IIM[70].

Several definitions for cancer-associated IIM exist with the most common being a cancer diagnosed within 2 to 3 years prior to or after the diagnosis of IIM, given the higher risk for cancer in this window period[142,170–172]. However, a sustained higher risk of cancer in IIM has

Table 5 | Selected case series (n≥15) on rituximab use in IIM[147-159]

Authors (year)	n	Subsets	MSA	# of cycles	Definition of clinical response	Results
Couderc et al.[147] (2011)	30	12 ASyS, 6 DM, 12 PM	10 anti-ARS 2 anti-SRP	Single (n=30)	>25% decrease in CK and/or daily glucocorticoid dose, and physician's opinion.	53% had a clinical response. No difference by MSA status.
Munoz-Beamud et al.[148] (2013)	16	5 DM, 2 PM, 4 ASyS, 5 OM	6 anti-ARS 2 anti-SRP	Single (n=13) 2 cycles (n=2) 3 cycles (n=1)	Complete response: no MITAX A and B features. Partial response: loss of some, but not all, MITAX A and B features.	At 1 year, 38% partial and 19% complete response.
Unger et al.[149] (2014)	18	12 PM, 5 DM, 1 OM	10 anti-ARS 3 anti-Mi2 1 anti-SRP	Single (n=10) 2 cycles (n=1) ≥3 cycles (n=7)	≥50% decrease in CK levels and daily glucocorticoid dose. If CK normal or glucocorticoid dose <20mg/day, ≥50% improvement in other parameter sufficient.	78% clinical response.
Andersson et al.[150] (2015)	24	24 ASyS	24 anti-ARS	Single (n=8) 2 cycles (n=7) ≥3 cycles (n=9)	Not defined.	Improvement in muscle strength and lung function.
Bauhammer et al.[151] (2016)	32	17 ASyS	17 anti-ARS	Mean 4.6 cycles	Resolution of baseline symptoms for >6 months.	94% clinical response.
Barsotti et al.[152] (2018)	26	15 PM, 9 DM, 2 IBM	5 anti-ARS 1 anti-SRP 1 anti-TIF1γ		Major: increase ≥15% in MMT8 and ≥30% CK reduction at 6 months. Minor: improvement ≥2/4 IMACS CSM, ≥15% increase in MMT8, ≥20% increase in PGA, ≥20% increase MYOACT, ≥30% CK reduction.	27% achieved minor and 31% major improvement at 6 months. Higher proportion of MSA+ patients achieved major improvement.

Doyle et al.[153] (2018)	15	15 ASyS	15 anti-ARS	Single (n=8) Repeated (n=17)	>10% decrease in CT severity scores and/or >10% increase in FVC.	88% improved chest imaging and 79% improved PFT.
De Souza et al.[154] (2018)	38	13 ASyS, 15 DM, 10 PM	13 anti-ARS 4 anti-Mi2	N/A	IMACS DOI at 1 year	73% clinical response. No difference by MSA status.
Langlois et al.[155] (2020)	28	28 ASyS	28 anti-ARS	Median 3 cycles	Pulmonary progression-free survival in the absence of treatment-related adverse events.	89% met endpoint at 6 months.
Ahn et al.[156] (2020)	16	10 DM, 6 PM	N/A	Single (n=13) 2 cycles (n=3)	>25% decrease in CK and/or daily glucocorticoid dose, and physician's opinion. Partial if 2/3.	44% partial and 25% complete response at 24 weeks
Santos et al.[157] (2021)	18	15 DM, 2 PM, 1 JDM	N/A	Single (n=5) 2 cycles (n=8) ≥3 cycles (n=5)	No disease activity for ≥6 months.	66% clinical response
Egeli et al.[158] (2022)	26	19 DM, 7 PM	N/A	Mean 4 cycles	Primary endpoint: improvement of symptoms. Secondary endpoint: decrease in CK levels.	Improvement in muscle strength and skin rashes.
Janardana et al.[159] (2023)	42	18 DM, 11 OM, 6 AsyS, 5 PM, 1 JDM, 1 IMNM	8 anti-ARS 4 anti-Mi2 2 anti-SRP 1 anti-MDA5	Single (n=42)	Improvement in IMACS CSM and IMACS total improvement score	94% achieved minimal improvement. No difference by MSA status.

ASyS, anti-synthetase syndrome; DM, dermatomyositis; JDM, juvenile dermatomyositis; PM, polymyositis; OM, overlap myositis; CK, creatine kinase; MSA, myositis-specific antibodies; MITAX, Myositis Intention to Treat Index; MMT, manual muscle testing; ILD, interstitial lung disease; SF-36, 36-Item Short-Form Survey; PFT, pulmonary function testing; DOI, definition of improvement; PGA, physician global assessment; CSM, core set measures; CT, computed tomography.

been demonstrated up to 10 years after diagnosis, with notable time trend differences in site-specific cancer with colorectal, lung and ovarian cancers being more frequent before diagnosis and oropharyngeal, cervical, and skin cancers more frequent after diagnosis[168]. Based on these findings, it can be hypothesized that mechanisms linking cancer and IIM might differ with time, perhaps being influenced by prolonged disease activity and long-term immunosuppression, variables that are seldom considered in studies investigating the association between cancer and IIM.

The autoantibody most strongly associated with cancer, anti-TIF1γ, targets a protein involved in cancer promotion[173]. In presence of a tumor expressing TIF1γ, the immune system potentially builds an anti-tumoral response extending to other organs by epitope spreading or molecular mimicry triggering IIM development[173,174]. However, not all anti-TIF1γ positive DM patients develop cancers and recent work demonstrated that the presence of multiple other circulating autoantibodies in those patients reduced the likelihood of cancer development[175]. The authors suggested a model where a strong anti-tumoral immune response would eliminate the cancer but promote autoimmunity resulting in DM development without cancer emergence. Despite those novel insights into the relationship between cancer and IIM, the optimal approach for the management of cancer-associated IIM remains unclear resulting in generally poor outcomes in that subset of patients.

Cardiovascular

Traditional cardiovascular risk factors such as diabetes, hypertension and dyslipidemia are more prevalent in chronic inflammatory diseases including IIM than in the general population[176,177]. Chronic inflammation contributes to accelerated atherogenesis and in line with this, decreased flow-mediated dilatation and increased arterial stiffness have been reported in individuals with IIM compared with healthy controls[178,179]. Patients with IIM have increased risks of stroke, coronary artery disease and heart failure[180–185]. A large Canadian population-based study showed a 3 to 4-fold increased risk of acute coronary syndromes (ACS) in IIM compared to the general population[181]. Still, no study in IIM has explored a possible competing risk of death that could bias the estimated risk of ACS. Moreover, stratification of ACS risk on sex has rarely been reported[186]. Cardiovascular complications being a leading cause of mortality in IIM, it is important to generate robust estimates of ACS risks and identify areas for quality-of-care improvement.

2.10 Mortality

Despite advances in the field and availability of novel treatments, mortality remains high in IIM. A large contemporary Norwegian cohort study reported standardized mortality rates of 2.4 for PM and 2.6 for DM[187]. Moreover, higher mortality was found with increasing age and anti-Ro positivity in PM, and with cancer and low diffusing capacity of the lung for carbon monoxide in DM[187]. A nationwide Swedish cohort study reported a mortality

rate of 60/1000 person-years in IIM with an all-cause mortality HR of 3.7 (95%CI 3.2-4.4) compared to the general population[188]. In that study, when estimates were stratified by time since diagnosis, the HR increased to 9.6 (95%CI 6.9-13.5) in the year after diagnosis. Cancer and cardiopulmonary diseases are common causes of death in IIM[187,188].

MSA can be helpful prognostic factors for IIM, although studies on this topic are limited by small sample sizes and heterogeneity within autoantibody-defined subsets[189]. For example, rapidly progressive ILD, Raynaud phenomenon and anti-MDA5 positivity were strongly associated with mortality in retrospective studies on IIM-ILD[190,191]. In anti-synthetase syndrome, an observational study reported a 10-year cumulative survival of 70% for anti-Jo1 subjects compared to 47% for non-anti-Jo1[192]. MAAs are not systematically screened for in clinic or reported in the literature but could potentially help refine clinical outcome prediction. Apart from the association of anti-Ro52 with more severe ILD and increased mortality, the phenotypes and clinical outcomes associated with other MAAs remain largely under-reported[151,187,193,194].

Table 6 | Retrospective studies on dysphagia and mortality[195-204]

Authors (year)	Population	Dysphagia ascertainment	Findings
Medsger et al.[195] (1971)	n=124 JDM, DM, PM	Chart review	Dysphagia associated with increased crude mortality risk ($p<0.01$).
Carpenter et al.[196] (1977)	n=62 PM	Chart review	At 1-year, higher proportion of death in the dysphagia group.
Benbassat et al.[197] (1985)	n=92 JDM, DM, PM	Chart review	Dysphagia not associated with increased mortality after adjustment.
Hochberg et al.[198] (1986)	n=76 DM, PM	Chart review	Dysphagia not associated with increased mortality after adjustment.
Maugars et al.[199] (1996)	n=69 DM, PM	Chart review	Dysphagia associated with decreased mortality.
Marie et al.[200] (2001)	n=77 DM, PM	Manometry	Esophageal dysfunction not associated with increased mortality.
Danko et al.[201] (2004)	n=162 JDM, DM, PM	Chart review	Dysphagia associated with increased crude mortality risk in PM, but not after adjustment.
Galindo-Feria et al.[202] (2016)	n=264 DM, PM	Chart review	Dysphagia not associated with increased mortality.
Ohmura et al.[203] (2022)	n=254 DM, PM	Chart review + questionnaire	Dysphagia not associated with increased mortality after adjustment.
Kim et al.[204] (2022)	n=88 DM, PM, OM, IBM*	VFSS	Dysphagia not associated with increased mortality.

JDM, juvenile dermatomyositis; DM, dermatomyositis; PM, polymyositis; OM, overlap myositis; IBM, inclusion body myositis; VFSS, videofluoroscopy swallowing study.

There is discordance in the IIM literature concerning the association between dysphagia and mortality (**Table 6**)[195-204]. Dysphagia is a risk factor for aspiration pneumonia as well as malnutrition and unadjusted estimates from earlier reports suggested increased mortality in subjects with IIM affected by dysphagia[195,196]. However, more recently, adjusted Cox proportional hazard models showed a null effect of dysphagia on mortality but reported increased mortality risks with each 10-year increase of age (HR 1.8 (95%CI 1.3-2.3)) and cancer-associated myositis (HR 3.1 (95%CI 1.6-5.9))[203]. In addition to possible confounding, an explanation for these contradictory reports could be that cancer has a modification effect on the relationship between dysphagia and mortality, a hypothesis that has not been explored to date.

2.11 Healthcare costs

Healthcare costs are categorized in direct and indirect costs. Direct costs refer to all costs directly linked with patient's care (e.g., outpatient visits, diagnostic procedures, hospitalization, medication). Indirect costs include work loss and reduction of work productivity. The costs generated by diagnostic investigations, outpatient visits and hospitalizations in IIM are significant[205-208]. Based on administrative data, the mean annual direct cost for prevalent IIM cases in 2008 Canadian dollars was estimated at $4099, with hospitalizations and physician visits accounting for most of these costs[205]. Using insurance claims, the mean annual direct costs of prevalent IIM were estimated at $15539 in 2009 US dollars[207]. While these studies used different case definitions which might explain the different estimates, both reported increased costs closer to diagnosis. Age, race, and sex are also reported to affect direct costs[205,209]. To date, there is no estimate of indirect costs in IIM even though in other systemic rheumatic diseases indirect costs often exceed direct costs[210-214]. Defining the economic burden of IIM is important to help improve resource allocation and identify areas of need for future research in the field.

3 Research aims

The research projects included in this thesis aim to expand our understanding of IIM risk factors and disease outcomes by leveraging several existing clinical registries and administrative databases. The specific research questions that motivated the projects were:

1. Are autoantibody profiles including both MSA and MAAs associated with distinct clinical features and HLA variants in IIM?
2. In IIM, is anti-ARS positivity associated with better clinical response to rituximab in a real-world setting?
3. Are IIM patients at higher risk of ACS compared to the general population?
4. Is there a modification effect of cancer on the association between exposure to dysphagia in early disease and mortality in IIM?
5. What are the direct and indirect healthcare costs in IIM and what are their trajectories over time?

4 Materials and methods

4.1 Data sources

Clinical registries

For **study I**, the MYONET registry (formerly Euromyositis; https://www.myonet.info/) was used to identify patients with IIM. This large international database records clinical features, and autoantibody profiles on more than 2 300 patients with IIM. MYONET is a web-based platform with harmonized data using pre-defined variables to facilitate multicenter collaborations[17]. For **study II**, the Swedish Rheumatology Quality Register was used to identify patients with IIM treated with rituximab. This national registry includes the SweMyoNet module where treating rheumatologists prospectively compile IIM diagnoses and outcome data since 2003. Every clinical visit is entered as a study visit allowing for detailed longitudinal disease activity assessments based notably on the IMACS core set measures[143]. For **study IV**, the Swedish Rheumatology Quality Register, the Canadian Inflammatory Myopathy Study (CIMS) and selected centers from the MYONET registry were approached to identify patients with IIM and documented dysphagia exposure within 6 months of disease onset. CIMS is a multicenter inception cohort of IIM patients with detailed demographic and phenotypic data, as well as longitudinal clinical assessments.

Population-based registries

All Swedish residents have a personal identification number which enables administrative database linkage to generate rich data sources for epidemiological research (**Figure 5**). In **studies III** and **V**, the Swedish National Patient Register, the Swedish Total Population Register, and the Swedish Cause of Death Register were used to identify patients with IIM and general population comparators[215–217]. The National Patient Register indexes data on hospitalizations since 1987 and outpatient visits since 2001 using International Classification of Disease (ICD) codes[215]. Clinicians assign a main diagnosis for each hospitalization with several possible contributory diagnoses. Most subjects with IIM (95%) are followed by hospital-based specialists, resulting in a high coverage of outpatient visits using the National Patient Register. The Swedish Total Population Register contains data on all Swedish residents since 1968 including date of birth, place of birth, sex, date of immigration and emigration, address, civil status, and death[216]. The Swedish Cause of Death Register compiles all deaths, with almost complete coverage of causes of death as reported on death certificates by ICD codes[217]. The Longitudinal Integration Database for Health Insurance and Labor Market Studies covers the adult Swedish population since 1990 and contains data on education, income, sick leave, disability pension and level of education. For **study V**, the Cancer Register and the Swedish Rheumatology Quality Register were used to extract data about cancer diagnoses and drug infusions that would not be captured by the Prescribed Drug Register[218].

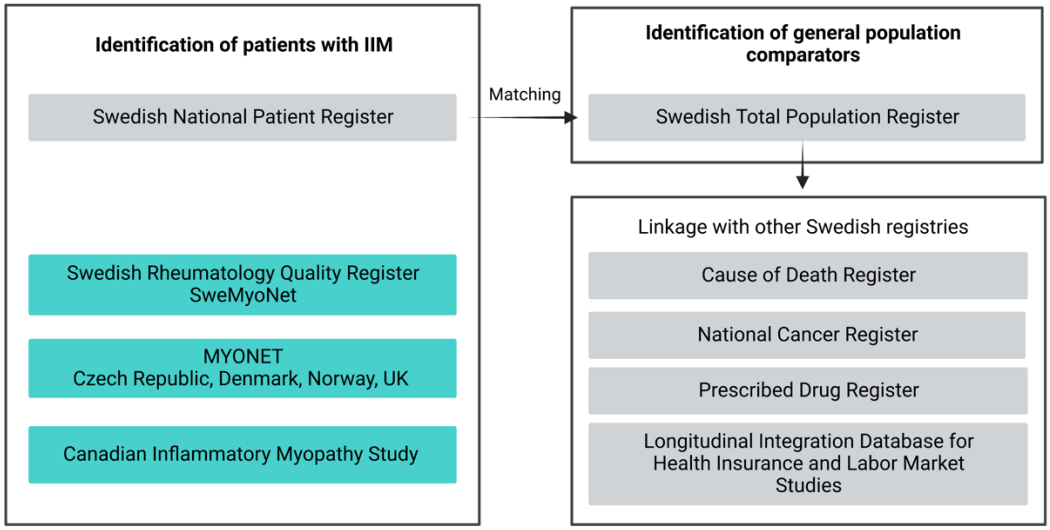

Figure 5 | Data sources used
The population-based data sources are depicted in grey and the clinical registries in cyan. Created with BioRender.

4.2 Populations

In **studies I**, **II** and **IV** based on clinical registries, inclusion relied on being classified with at least a probable IIM per the 2017 EULAR/ACR IIM classification criteria[94]. Given that overlap myositis and anti-synthetase syndrome are not captured as separate entities using this approach, these subsets were further subclassified based on the definitions of Bohan and Peter and Connors et al., respectively[77,81,82].

For **studies III** and **V** based on administrative databases, patients with IIM were identified through the National Patient Register using ICD-10 codes (Juvenile DM M33.0, DM M33.1 & M33.9, PM M33.2, IBM G72.4). This case definition previously showed a positive predictive value and a sensitivity of >85% for all ICD codes except IBM[219,220]. Once identified, the cases were required to have: 1) ≥2 visits indexed with an IIM diagnosis by a specialist (dermatologist, internist, neurologist, or rheumatologist), 2) an initial visit during the study period, and 3) a follow-up visit within one year of that initial visit listing an IIM code. If an IIM code was detected in the year prior to the study period, patients were excluded, such that only incident cases would be included. This approach is accurate for DM identification, but as ICD codes fail to accurately differentiate other IIM subsets the remaining patients were labelled "other IIM" and could include PM, IMNM, overlap myositis and/or IBM. Once identified the patients with IIM were matched with general population comparators that were assigned the same index date.

4.3 Disease activity assessment

Study IV used the Myositis Disease Activity Assessment Tool (MDAAT) to assess disease severity. This tool has been used in major IIM clinical trials and is a validated and reliable instrument to assess disease activity in muscular and extramuscular domains[142,160,221,222]. It

is divided in the Myositis Intention to Treat Index (MITAX) and the myositis disease activity assessment visual analog scales (MYOACT). **Study II** used the 2016 ACR/EULAR improvement criteria for IIM to assess rituximab effectiveness (**Table 7**)[223]. These criteria assign weights to the absolute percent change in the six IMACS core set measures to calculate a total improvement score categorized as minimal (≥20), moderate (≥40) or major (≥60). This replaced the previous definition of improvement used in clinical trials where improvement was defined as three out of six of the core set measures improved by ≥20%, with no more than two worse by ≥25% (excluding manual muscle testing)[143].

Table 7 | 2016 ACR / EULAR response criteria[223]

Core set measures	Improvement score
Physician global activity	
Worsening to 5% improvement	0
>5–15% improvement	7.5
>15–25% improvement	15
>25–40% improvement	17.5
>40% improvement	20
Patient global activity	
Worsening to 5% improvement	0
>5–15% improvement	2.5
>15–25% improvement	5
>25–40% improvement	7.5
>40% improvement	10
Manual muscle testing	
Worsening to 2% improvement	0
>2–10% improvement	10
>10–20% improvement	20
>20–30% improvement	27.5
>30% improvement	32.5
Health Assessment Questionnaire	
Worsening to 5% improvement	0
>5–15% improvement	5
>15–25% improvement	7.5
>25–40% improvement	7.5
>40% improvement	10
Muscle enzymes (most abnormal)	
Worsening to 5% improvement	0
>5–15% improvement	2.5
>15–25% improvement	5
>25–40% improvement	7.5
>40% improvement	7.5
Extramuscular activity	
Worsening to 5% improvement	0
>5–15% improvement	7.5
>15–25% improvement	12.5
>25–40% improvement	15
>40% improvement	20

The absolute percent change is calculated for each core set measure which are added to obtain the final score. Range 0–100 with higher scores indicating a greater degree of improvement.

4.4 Autoantibody profiles

Different autoantibody detection methods were used for **studies I**, **II** and **IV** depending on local availability and practices. This reflects the lack of standardization for MSA/MAA detection and international standard of care as shown by a survey from the IMACS Myositis Autoantibodies Scientific Interest Group reporting that their members used enzyme immunoassays (46%), line blot immunoassays (37%), and less frequently immunoprecipitation to screen for MSA[224]. Enzyme-linked immunosorbent assays (ELISA) are sensitive plate-based assays that allow for quantitative measurement of MSA/MAA[225]. Line blot immunoassays allow for simultaneous screening of several MSA/MAA by combining multiple antigens on coated membranes positioned on chips on a single strip and staining intensity when positive gives a semi-quantitative measure of the autoantibody concentration in the sample. Comparative studies have reported on the performance of ELISA and line blot immunoassays compared to immunoprecipitation and some problematic specificities were reported with notably poor performance of line blot immunoassays for rare anti-ARS (e.g., anti-OJ), and -TIF1γ[226,227]. Immunoprecipitation, despite being labor intensive, limited to a small number of specialized laboratories and unable to detect certain specificities (e.g., anti-Ro52), remains the reference standard for MSA detection[228,229].

4.5 Specific studies

4.5.1 Study I

→ **Are autoantibody profiles including both MSA and MAAs associated with distinct clinical features and HLA variants in IIM?**

Study design and population

A multicenter cross-sectional study including adult patients classified as possible IIM from the MYONET registry was conducted[94]. Patients with complete autoantibody profiles and available genotyping of *HLA-DRB1*, *HLA-DQA1*, and *HLA-DQB1* alleles were selected. Demographic characteristics, clinical features, serological profiles, and genotyping data were extracted for analyses.

Autoantibody-defined clusters

Given the inclusion of patients with IIM from several institutions in different countries, an algorithm for determination of serological profiles was developed. If more than one method was used for a same individual with discordant results, the measurement time point closer to diagnosis was kept, prioritizing immunoprecipitation if available as it remains the reference standard in the field. Using autoantibody profiles including both MSA and MAAs, clusters were generated using an unsupervised machine learning approach that, based on pattern recognition, groups patients with similar autoantibody profiles together. Gower's distance was used to measure dissimilarity between

dichotomous observations (i.e., the presence or not of a particular autoantibody) [230]. A final distance matrix was obtained and the partitioning around medoid algorithm was used to create the clusters[231]. The medoid of each cluster represents the observation (or individual) that yielded the lowest average distance. This method is robust to outliers and easy to conceptualize as the center of each cluster can be represented by an individual patient. The number of clusters was selected using the silhouette method. The cluster analysis was performed with the *cluster* package in R[232].

Genotyping and amino acid determination

HLA-DRB1, *HLA-DQA1*, and *HLA-DQB1* alleles were directly genotyped using either Illumina immunochip array, Luminex multiplex assay, or sequence-specific primer polymerase chain reaction assay (DR low-resolution kit; Olerup SSP)[116,126,233]. Moreover, amino acid variations for HLA class II and I were imputed from the Dissect Consortium data for the UK and Scandinavia (i.e., Sweden, Denmark, and Norway) using the SNP2HLA software and the Type 1 Diabetes Genetics Consortium reference panel[234].

Statistical analyses

Logistic regressions were used to explore the associations between autoantibody-based subgroups and clinical features, HLA class II alleles, and imputed amino acid frequencies. Logistic regressions are useful to study relationships between binary dependent variables (e.g., belonging to a certain autoantibody-defined subgroup) and one or more independent variables (e.g., having ILD, carrying a certain HLA allele). In the models for associations between clinical features and autoantibody-defined subgroups, the binary outcome was belonging to one of the individual subgroups (e.g., subgroup 1) vs. belonging to the rest of the cohort. Regression models were adjusted for age, sex and recruiting centers.

Logistic regression models for genetic associations were applied separately by regions and subsequently meta-analyzed to address potential heterogeneity between centers by geographical regions. The p-values for genetic associations were adjusted using the Benjamini & Yekutieli step-up method for false discovery rate (FDR) with a threshold for significance at 5%[235]. The FDR relates to the concept of type I error (i.e., rejecting a null hypothesis that is true) and represents the proportion of discoveries that are falsely rejected. Additionally, conditional logistic regressions were performed to identify independent genetic association signals. After identification of the strongest association signals using logistic regression, new models were built using the allelic dosage of these variants as covariates; if the target association remained significant, independence was assumed. Conditional analyses were cumulative, meaning that each step considered the full effect of the genetic variants in the previous step, starting with the strongest associated alleles. The models were further adjusted for sex, age, and geographical

regions. The genetic association analyses were performed using PLINK and all other statistical analyses performed using R[236-238].

4.5.2 Study II

→ **Is anti-ARS positivity associated with better clinical response to rituximab in IIM in a real-world setting?**

Study design and population

A cohort study including adult subjects with IIM from the Swedish Rheumatology Quality Register exposed to at least one cycle of rituximab from 1994 to 2017 was conducted (**Figure 6**). Patients with a baseline visit 0-2 months before their first rituximab exposure and a follow-up assessment 5-10 months after their first rituximab exposure were included for effectiveness assessment. An induction rituximab cycle was defined as a dose between 500mg to 1000mg given two weeks apart or 750mg/m2 weekly for two doses or 375mg/m2 weekly for four doses, and maintenance as any following administration separated from the previous cycle by more than three months.

Disease activity and safety assessments

Effectiveness assessment was done at 5-10 months after the first and last cycles. Demographic variables, autoantibody profiles and clinical features at diagnosis were collected. Available IMACS core set measures were recorded at each time point. Minimal (≥20), moderate (≥40) and major (≥60) improvement scores were calculated using the 2016 ACR/EULAR criteria for clinical response in IIM[223].

Adverse events considered to be related to rituximab (grade ≥2) and mortality from any cause were recorded from baseline visit to one year after last rituximab exposure for all patients. The Common Terminology Criteria for Adverse Events grading for severity was used with a grade 2 being defined as moderate symptoms associated with functional limitations that would require local or noninvasive intervention[239].

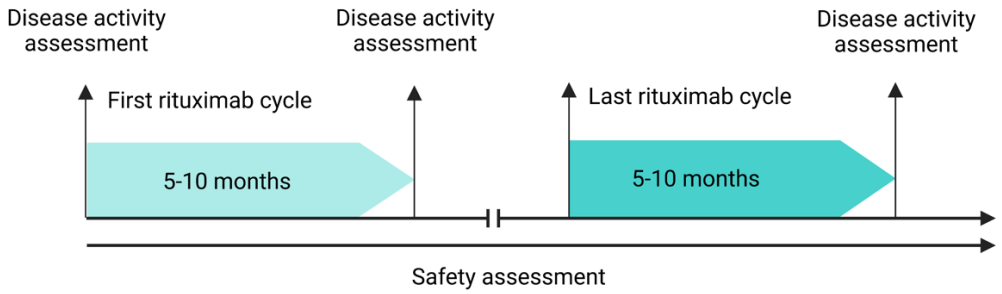

Figure 6 | Design study II
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Statistical analyses

Baseline disease activity measures of anti-ARS positive patients were compared to anti-ARS negative patients after their first and last rituximab cycles. Each anti-ARS defined group was also compared longitudinally (baseline vs first cycle and baseline vs last cycle). Comparisons were done using Student's *t* or Mann-Whitney U tests for continuous variables, and Fisher exact test for categorical variables. A logistic regression model was used to explore the association between anti-ARS positivity and moderate/major disease improvement after one rituximab cycle. The model was adjusted for age, sex, disease duration, and disease severity at baseline. Severe disease at baseline was considered present if a patient was on an equivalent of prednisone ≥20 mg/day in combination with at least one other immunosuppressant at the time of rituximab introduction.

4.5.3 Study III

→ **Are IIM patients at higher risk of ACS compared to the general population?**

Study design and population

A cohort study including incident patients with IIM identified from the Swedish National Patient Register from 2002 to 2011 using the case definition previously outlined was conducted (**Figure 7**). Individuals with IIM were matched up to 1:10 on age, sex, and place of residence with general population comparators from the Swedish Population Register. The index date for IIM cohort entry was the date of the second visit with an IIM code recorded. The follow-up ended at ACS occurrence, first emigration, death, or December 31st, 2013, whichever occurred first.

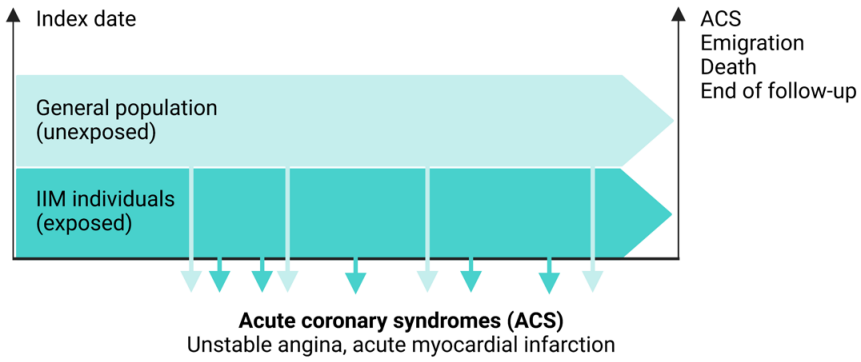

Figure 7 | Design study III
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Outcome

The occurrence of the first-ever ACS during the follow-up period was determined using ICD-10 codes (I20.0 unstable angina, I21.0-I21.4 & I21.9 for non-ST-elevation (NSTEMI) and ST elevation myocardial infarction (STEMI)) from the Swedish National Patient Register primary discharge diagnosis and Cause of Death Register. This definition of ACS showed

a positive predictive value of 95% in prior studies[240,241]. Individuals with ACS prior to index date were excluded.

Covariates

Demographic data were extracted from the Swedish Population Register. Baseline cardiovascular comorbidities and risk factors were obtained from the Swedish National Patient Register based on ICD-10 codes (I20.9 stable angina, E10-11 diabetes, I10-I13 & I15 hypertension, I42 & I50 heart failure, I48 atrial fibrillation, I61 & I63 stroke) in the year preceding the index date. The Prescribed Drug Register was used to identify exposure to medications used to treat cardiovascular diseases/risk factors or known to increase cardiovascular risk in the 6 months preceding the index date. Exposure to immunosuppression ± two months from the index date was also determined using the Prescribed Drug Register. Educational level data was extracted from the Longitudinal Integration Database for Health Insurance and Labor Market Studies register.

Statistical analyses

Crude mortality rates and 95%CI were calculated using the Poisson distribution and stratified by sex, age at diagnosis, and IIM subsets[242]. Cox proportional hazards models were generated to compare time from index date to first ACS in IIM (exposed) and the general population (unexposed). Cox proportional hazard models are frequently used for survival analyses as they estimate the simultaneous effect of several factors on the rate of an outcome (e.g., ACS) at a particular point in time[243]. Cox proportional hazard models estimate the relative magnitude of the effect of a variable on the rate of an outcome with the assumption that the rates in the exposed and unexposed groups are proportional over time. In addition to assuming constant estimated effects over time, Cox proportional hazard models also assume constant estimated effects across all levels of covariates. In this study, the Cox proportional hazard models were adjusted for age at index date as a continuous variable, birth year, year of IIM diagnosis, sex, and residential area.

As patients with IIM are at increased mortality risk, there was a possibility that they could die before experiencing the outcome of interest (i.e., competing risk of death). Censoring individuals who died could in this case violate the central assumption of non-informative censoring by assuming that they have the same ACS risk than those who remain alive. In the presence of a suspected competing event, two different hazard functions can be defined: the cause-specific hazard function and the sub-distribution hazard function which differ by risk sets (**Figure 8**)[244]. In our case, the cause-specific hazard function is the instantaneous rate of occurrence of ACS in individuals who are *alive* and event-free. The sub-distribution hazard function is the instantaneous rate of occurrence of ACS in individuals who are event-free even if they died. Sub-distribution HR and cumulative

incidence in **study III** were estimated using Fine and Gray competing risk regression models[245].

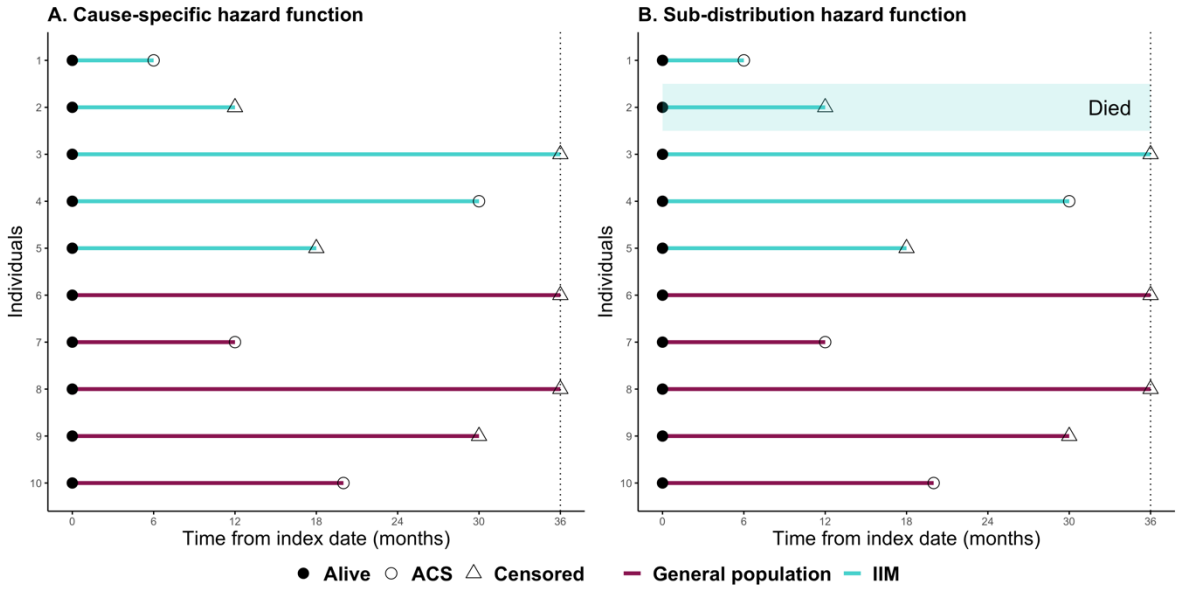

Figure 8 | Cause-specific and sub-distribution hazard functions
Panel A represents 10 fictional subjects, 5 exposed to IIM (blue) and 5 unexposed (purple). Two patients in each group experienced an ACS during the follow-up period (circles). Two were censored before end of follow-up in the IIM group and one in the unexposed (triangles). Panel B reveals that patient #2, censored in panel A, died early in the follow-up period. Patient #2 would be removed from the risk set to estimate the cause-specific hazard function but would remain in the risk set to estimate the sub-distribution hazard function.

4.5.4 Study IV

→ **Is there a modification effect of cancer on the association between dysphagia and mortality?**

Study design and population

A multicenter cohort study of incident adult patients with at least a possible IIM and documented presence or absence of dysphagia within 6 months of disease onset was conducted (**Figure 9**)[94]. Patients with IIM were identified from clinical registries in Canada, the Czech Republic, Denmark, Norway, and Sweden. Subjects were censored if lost to follow-up or if the outcome (death) did not occur by the end of the 5-year follow-up period.

Exposure and outcome

Dysphagia was defined as difficulty in swallowing and/or objective evidence of esophageal dysmotility as assessed by study physician[17]. Death due to any cause was collected and, if possible, confirmed with a next of kin or a linkage to a national death registry.

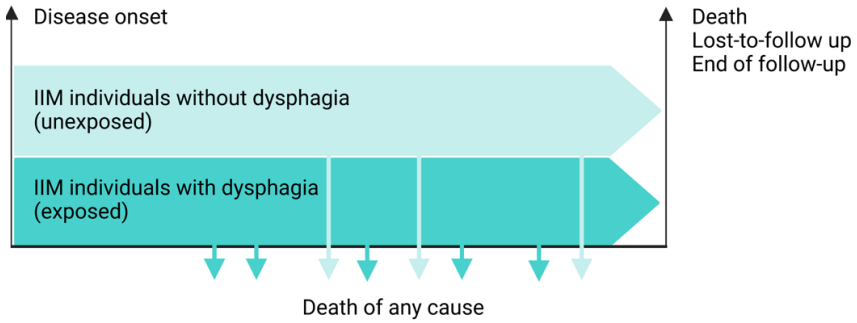

Figure 9 | Design study IV
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Covariates

Demographic variables and baseline clinical features assessed by study physicians were collected from the different clinical registries. Disease was considered severe at baseline if: 1) patients were treated with IV cyclophosphamide or corticosteroid pulses, 2) any organ involvement (excluding dysphagia) was scored as severe in the MDAAT or, 3) diaphragmatic weakness, myocarditis, or severe arrhythmias were present.

Statistical analyses

Crude mortality rates and 95%CI were calculated using the Poisson distribution. Kaplan-Meier survival curves were generated, and differences compared with log rank tests. Kaplan-Meier is a non-parametric method to calculate the unadjusted probability to have survived at a given time. The Kaplan-Meier considers only one survival predictor, in this instance being exposed to dysphagia in the first 6 months of disease onset. Cox proportional hazards model were used to assess the effect of dysphagia on survival while adjusting for possible confounders such as age at diagnosis, sex, and IIM subset.

Confounding arises when other variables influence both the exposure and the outcome. For example, age can affect the risk of developing a medical condition such as dysphagia and is a major risk factor for death. Age in this example is a confounder. In contrast, an exposure can have different effects on the outcome depending on the different levels of another variable which is called effect modification[246]. In our case, the hypothesis was that dysphagia (exposure) could have different effects on mortality (outcome) depending on the presence or not of cancer (modifier).

To explore possible effect modification of cancer on the association between dysphagia in early disease and all-cause mortality, a Cox proportional hazard model stratified on cancer status including an interaction term between dysphagia and cancer was used[247]. This model allowed for different baseline hazard functions in each stratum (cancer / no cancer). To test if cancer status had an interaction with variables other than dysphagia in the model, separate Cox proportional hazard models were performed on patients unexposed and exposed to cancer. As with the Cox proportional hazard model stratified

on cancer status, this approach allowed for different baseline hazard functions in each group while accounting for possible differential effect of cancer status on variables included in the models. Robust variance estimators were used to compute the 95%CI and proportional hazards assumption were tested using the scaled Schoenfeld residuals[238].

Given the small number of patients included and expected number of events (death), adjustment for confounding was also performed using inverse probability weighting (IPW) for the stratified Cox proportional hazard model using the *WeightIt* package in R[248]. The goal of IPW is to create pseudo-populations with equal distribution of confounders between groups. This data reduction technique is useful when many confounders are considered and/or when a small number of events are expected. Compared to other propensity score approaches, IPW has the advantage of increasing effective sample size by keeping all subjects in the analysis and generates more accurate HR estimates[249]. In our case, the weights were estimated using age at diagnosis, sex, IIM subsets, and cancer status at baseline. Stabilized weights were used to limit the variability of the estimated weights[250]. In case of potential misspecification of the model used to create the weights, all covariates in the main model were included in the IPW-weighted model to obtain "doubly robust" estimates[251]. Covariate balance for the weighted samples was assessed using standardized differences with a threshold of 0.05.

4.5.5 Study V

→ **What direct and indirect healthcare costs are generated in IIM and what are their trajectories with time?**

Study design and population

A serial cross-sectional study including incident patients with IIM identified from the Swedish National Patient Register from 2010 to 2016 based on the case definition previously outlined was conducted (**Figure 10**). Patients with IIM were matched up to 1:5 on age, sex, and place of residence with general population comparators from the Swedish Population Register. The index date used for the IIM cohort entry was the date of the second recorded visit.

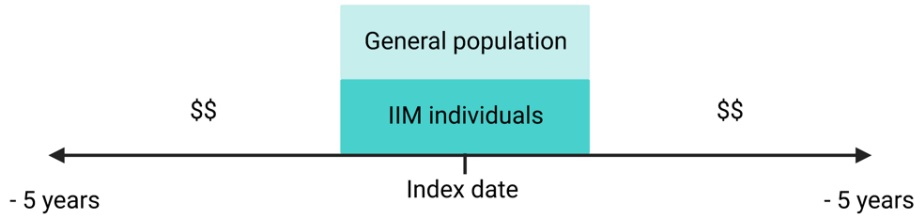

Figure 10 | Design study V
Healthcare costs were estimated yearly for 5 years before and after index date.
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Healthcare costs

Hospitalizations and outpatient specialist visits were identified from the National Patient Register using ICD-10 codes (main diagnosis and up to 25 contributory diagnoses). Costs were calculated using the Disease Related Group coding system that assigns weights based on main and contributory diagnoses, procedures, comorbidities/complications, sex, age, and discharge status[252]. The weights represent an average of healthcare-related costs assigned to a specific diagnostic-related group and are applied to the standard rates associated with specific medical outpatient visits or hospitalizations. Medications were retrieved from the Prescribed Drug Register. Data on parenteral biologic agents were collected from the Swedish Rheumatology Quality Register and assigned a price using the Medicine Compendium for healthcare professionals (FASS 2019)[253]. Sick leave and disability pension data were retrieved from the Social Insurance Agency. Sick leaves of a duration less than two weeks were not captured as their coverage is ensured by employers. Productivity loss was estimated by the Human Capital Approach (loss of productivity = loss of earnings) using all workdays lost multiplied by the average monthly Swedish salary for 2019 (~€3052 including taxes (31.42%))[254].

Statistical analyses

Cancer-associated IIM (diagnosis of cancer occurring ± 3 years from IIM diagnosis), sex and age of retirement in Sweden (65 years) were used to stratify the cohort. Mean annual costs stratified by age, sex and cancer status were estimated. Productivity loss was assessed only in the 18 to 64 years age group.

4.6 Ethical considerations

All clinical registries received approval from their local ethical review boards and obtained written informed consent from study participants. The data linkage for the Swedish administrative databases received approval from the Swedish Ethical Review Authority. Some ethical concerns when conducting registry-based studies relate to confidentiality, respect of privacy and autonomy. The databases used to conduct the projects included in this thesis contain sensitive personal data, that, if leaked, could harm subjects, and violate their right to privacy. Thus, data were anonymized and coded before being securely stored and analyzed. For clinical registry studies, the keys of the subject's code were kept on secure networks and only accessed by authorized personnel. These measures are important as breach of confidentiality is a concern in clinical research in rare diseases, as it could be easier to identify subjects with limited information. Despite this minimal risk, observational studies are crucial to improve clinical outcomes in IIM.

Clinical registries rely on referrals from other physicians for recruitment. In some cases, the treating rheumatologists also conduct the research visits. It could be argued that some subjects could feel pressured to be part of the registries, affecting their autonomy. However, in the course of obtaining informed consent, the voluntary nature of the

patients' participation in the registries is explained as well as the possibility to withdraw at any time. An advantage of combining study visits with usual care visits is that it decreases the burden on the study participant of attending extra visits to participate in the registries. For some, this can facilitate their ability to contribute to advancing research for themselves and their community.

5 Results

5.1 Study I

→ **In IIM, autoantibody profiles including both MSA and MAAs are associated with distinct HLA variants.**

Population

We identified 1348 patients with IIM and complete autoantibody profiles from the UK (54%), Scandinavia (31%) and the Czech Republic (16%). Clinical subsets included DM (28%), PM (20%), anti-synthetase syndrome (24%), overlap myositis (12%), IBM (11%), IMNM (4%), juvenile DM (1%), and undefined IIM (n=4) with similar distribution across centers. IIM patients positive for at least one of the tested autoantibodies (n=829) were included in the cluster analysis and seven autoantibody-defined subgroups were selected (**Table 8**). The patients negative for all tested autoantibodies (n=519) comprised the eight subgroup.

Clinical associations

Subgroups 3 (anti-PM/Scl dominated), 4 (anti-Mi2 dominated) and 7 (anti-TIF1γ dominated) were more likely to have DM rashes while subgroups 6 (anti-Jo1/Ro52 dominated) and 8 (negative for tested autoantibodies) were less likely to have DM rashes (**Figure 11**). Similarly, subgroup 6 (anti-Jo1/Ro52 dominated) was more likely to have Raynaud while subgroup 8 (negative for tested antibodies) was less likely to present this feature.

Subgroups	Clinical features	Odds Ratio (95% CI)
3 | anti-PM/Scl	DM rashes	2.6 (1.3-5.9)
4 | anti-Mi2	DM rashes	7.8 (2.8-33)
6 | anti-Jo1/Ro52	DM rashes	0.4 (0.2-0.7)
6 | anti-Jo1/Ro52	Raynaud	3.3 (1.2-11)
7 | anti-TIF1y	DM rashes	10 (3.1-65)
7 | anti-TIF1y	ILD	0.2 (0.1-0.4)
8 | none	DM rashes	0.5 (0.4-0.8)
8 | none	Raynaud	0.6 (0.4-1)

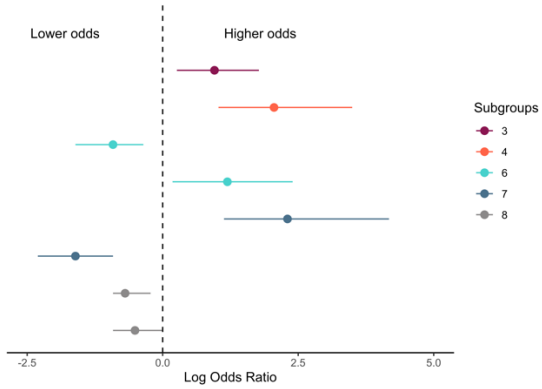


Figure 11 | Significant clinical associations with autoantibody-defined subgroups
DM, dermatomyositis; ILD, interstitial lung disease. OR reported for DM rashes are the OR for the presence of Gottron's papules/rashes.
Models adjusted for sex, age and center. Level of significance p <0.05.

Genetic associations

Differential genetic associations were found for almost all autoantibody-defined subgroups (**Figures 12-13-14, Table 9**) and those remained significant after correction for multiple comparisons. Genetic associations stratified by region (i.e., UK, Scandinavia, and the Czech Republic) showed a low degree of inconsistency (Q) and variation (I^2).

Table 8 | Characteristics of the eight autoantibody-defined subgroups

	Subgroups							
	1	2	3	4	5	6	7	8
Medoids	**Anti-Ro52**	**Anti-U1-snRNP**	**Anti-PM/Scl**	**Anti-Mi2**	**Anti-Jo1**	**Anti-Jo1/Ro52**	**Anti-TIF1γ**	**None†**
n	137 (10)	183 (14)	107 (8)	65 (5)	119 (9)	140 (10)	78 (6)	519 (39)
Female	93 (68)	116 (63)	79 (74)	45 (69)	76 (64)	96 (69)	64 (82)	313 (60)
Age diagnosis (years), median [IQR]	56 [48-64]	52 [39-62]	51 [38-63]	57 [47-69]	48 [35-58]	52 [40-60]	54 [43-65]	58 [46-68]
Muscle weakness	120 (88)	170 (93)	90 (84)	59 (91)	108 (91)	130 (93)	70 (90)	480 (93)
ILD	50 (37)	48 (26)	44 (41)	7 (11)	84 (71)	109 (78)	7 (9)	58 (11)
Mechanic's hand	23 (17)	20 (11)	46 (43)	14 (22)	32 (27)	52 (37)	17 (22)	27 (5)
Gottron's	31 (23)	57 (31)	44 (41)	43 (66)	27 (23)	27 (19)	63 (81)	89 (17)
Heliotrope	37 (27)	57 (31)	33 (31)	42 (65)	22 (19)	12 (9)	59 (76)	86 (17)
Calcinosis	6 (4)	7 (4)	8 (8)	0	0	3 (2)	6 (8)	12 (2)
Raynaud	37 (27)	74 (40)	51 (48)	14 (22)	37 (31)	53 (38)	10 (13)	82 (16)
Arthritis	33 (24)	60 (33)	29 (27)	14 (22)	65 (55)	83 (59)	10 (13)	101 (20)
Dysphagia	58 (42)	78 (43)	52 (49)	31 (48)	26 (22)	39 (28)	41 (53)	191 (37)
Anti-Jo1	0	6 (3)	0	1 (2)	119 (100)	140 (100)	0	0
Anti-PL7	7 (5)	13 (7)	0	0	0	0	0	0
Anti-PL12	5 (4)	3 (2)	1 (1)	0	1 (1)	0	0	0
Anti-EJ	2 (2)	0	0	0	0	0	0	0
Anti-OJ	0	7 (4)	0	0	0	0	0	0
Anti-TIF1γ	10 (7)	2 (1)	2 (2)	0	0	0	78 (100)	0
Anti-Mi2	1 (1)	1 (1)	1 (1)	65 (100)	0	2 (1)	0	0
Anti-SAE1	8 (6)	23 (13)	0	0	0	0	0	0
Anti-NXP2	1 (1)	23 (13)	1 (1)	0	0	0	0	0
Anti-MDA5	9 (7)	10 (6)	1 (1)	1 (2)	0	1 (1)	0	0
Anti-SRP	8 (6)	32 (18)	0	0	0	0	0	0
Anti-Ro52	137 (100)	16 (9)	0	0	0	140 (100)	0	0
Anti-PM/Scl	11 (8)	1 (1)	107 (100)	0	0	0	0	0
Anti-U1-snRNP	0	79 (43)	0	0	0	3 (2)	0	0

n (%) if not otherwise specified. †None of the autoantibodies tested for.
ILD, interstitial lung disease.

Autoantibody-defined subgroups	Genetic associations
1 | anti-Ro52 (10%)	No significant associations
2 | anti-U1-snRNP (14%)	*DQA1*03, DQB1*03, DRB1*04, DRB1*11, DRB1*15*, DRB1:pos13:SYF
3 | anti-PM/Scl (8%)	*DQA1*05, DQB1*02, DRB1*03*, DRB1:pos10:A,DRB1:pos26:F, DRB1:pos37:NL, DRB1:pos71:K
4 | anti-Mi2 (5%)	*DQA1*02, DRB1*07, DRB1*16*, A:pos74:H, DRB1:pos13:HY, DRB1:pos30:YHG, DRB1:pos37:SF
5 | anti-Jo1 (9%)	*DRB1*03*, B:pos9:D, DRB1:pos37:N
6 | anti-Jo1/Ro52 (10%)	*DQA1*05, DQB1*02, DRB1*03*, B:pos156:D, B:pos97:SW, C:pos66, DQB1:pos10:S, DRB1:pos37:N, DRB1:pos74:AQ
7 | Anti-TIF1y (6%)	*DQA1*02, DQB1*05, DRB1*01, DRB1*07*, A:pos70, A:pos9:F, DQB1:pos135:G, DQB1:pos74:S, DRB1:pos11:GL, DRB1:pos30:CH, DRB1:pos71:R, DRB1:pos74:QL, DRB1:pos96:HQ
8 | none (39%)	*DQA1*01, DQB1*06, DRB1*13*, B:pos114:DK, B:pos45:E, B:pos95:I

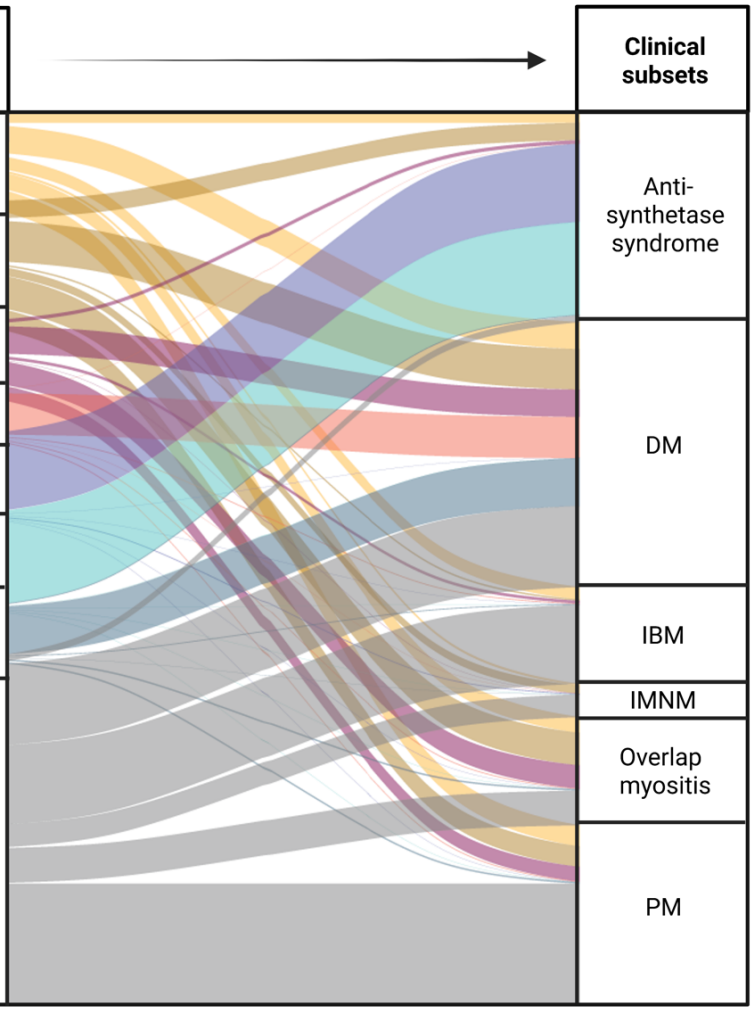


Figure 12 | Relationship between autoantibody-defined subgroups, HLA associations and clinically/pathologically-defined subsets
DM, dermatomyositis; IBM, inclusion body myositis; IMNM, immune-mediated necrotizing myopathy; PM, polymyositis.

Subgroup 1 (anti-Ro52 dominated) was heterogeneous in terms of serological profiles although all patients were positive for anti-Ro52. After correction for multiple testing, no significant genetic associations were observed for this subgroup.

Subgroup 2 (anti-U1-snRNP dominated) with 43% of anti-U1-snRNP, was also serologically heterogeneous. *HLA-DQA1*03*, *HLA-DQB1*03* *HLA-DRB1*04*, *HLA-DRB1*11*, and *HLA-DRB1*15* alleles were overrepresented in this subgroup, while no signal after correction was detected for class I amino acids. The conditional analyses showed that the *HLA-DRB1*15* association was independent of the *HLA-DRB1*04*, *HLA-DRB1*11*, *HLA-DQA1*03*, and *HLA-DQB1*03* signals (**Table 9**).

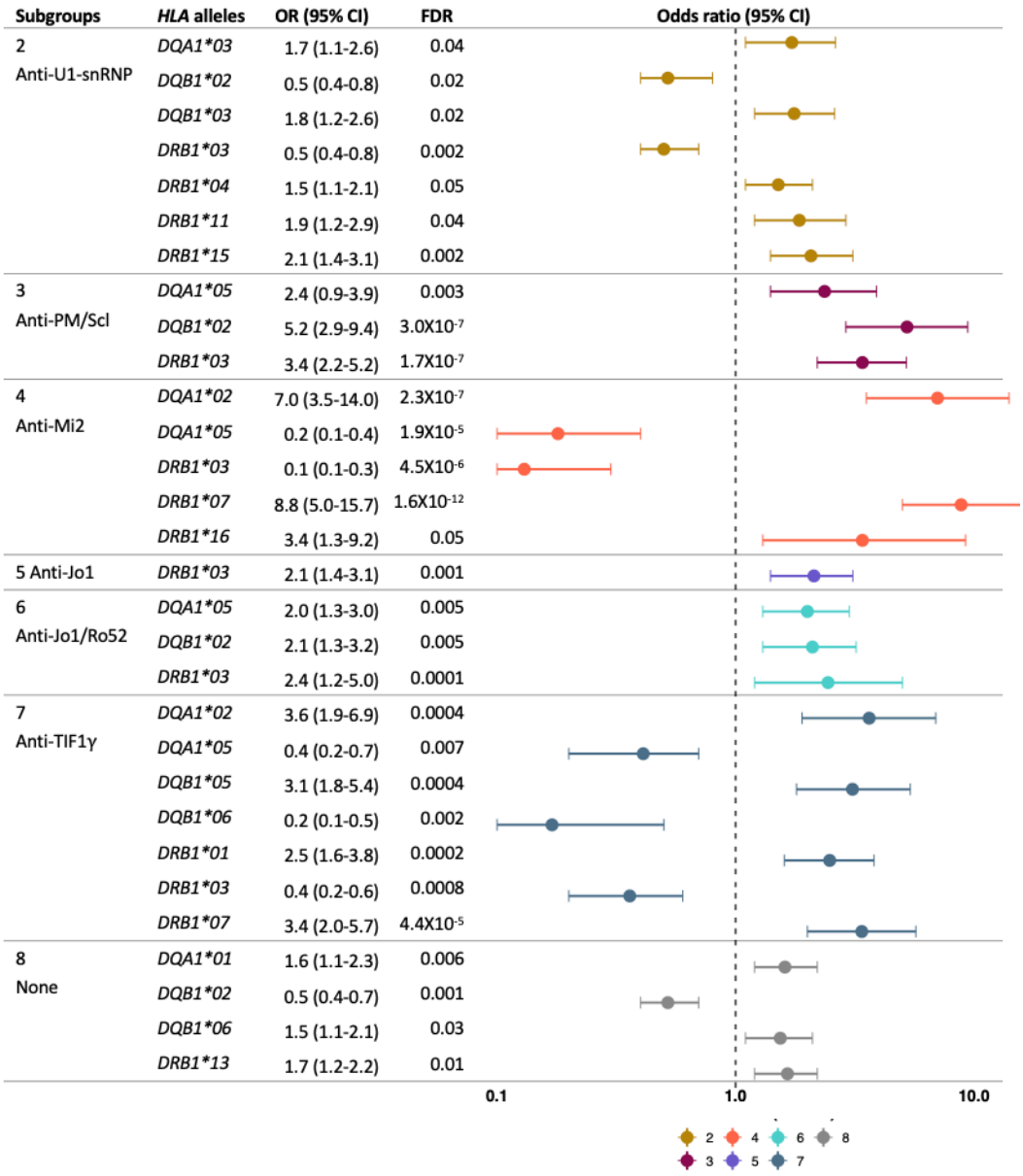


Figure 13 | Significant associations of *HLA-DQA1*, *HLA-DQB1* and *HLA-DRB1* alleles with autoantibody-defined subgroups from the meta-analyses of geographical regions
FDR, false discovery rate.

Table 9 | Selected results from the conditional regression analysis

Subgroups	Conditional on	Alleles	OR (95% CI)	FDR
2 – anti-U1-snRNP	*DRB1*15*	*DQA1*03*	2.5 (1.4-4.7)	0.009
		*DQB1*02*	0.4 (0.2-0.7)	0.009
		*DQB1*03*	2.8 (1.6-4.8)	0.003
		*DRB1*03*	0.4 (0.2-0.6)	0.003
		*DRB1*04*	2.1 (1.3-3.2)	0.005
		*DRB1*11*	2.6 (1.5-4.6)	0.005
6 – Anti-Jo1/Ro52	*DRB1*03*	*DQB1*02*	0.3 (0.1-0.9)	0.48

FDR, false discovery rate.

Subgroup 3 (anti-PM/Scl dominated), with all patients positive for anti-PM/Scl, showed significant associations with class II alleles (*HLA-DRB1*03, HLA-DQA1*05*, and *HLA-DQB1*02*) and class II amino acids (**Figures 13 & 14**).

Subgroup 4 (anti-Mi2 dominated) with all patients positive for anti-Mi2, had strong associations in terms of OR (95%CI) with *HLA-DQA1*02* and *HLA-DRB1*07*. Associations with glutamine (Q) at position 74 of HLA-DRB1, encoded by *HLA-DRB1*07:01*, and signals from HLA-A were also detected.

Subgroup 5 (anti-Jo1 dominated), with all patients positive for anti-Jo1, had the lowest median age at diagnosis with 48 years [IQR 35-58]. *HLA-DRB1*03* was positively associated with this subgroup, as well as arginine (R) at position 74 of HLA-DRB1 and aspartic acid (D) at position 9 of HLA-B.

Subgroup 6 (anti-Jo1/Ro52 dominated), with all patients positive for anti-Jo1 and anti-Ro52, had associations with *HLA-DQA1*05*, *HLA-DQB1*02* and *HLA-DRB1*03* alleles, arginine (R) at position 74 of HLA-DRB1 and aspartic acid (D) at position 9 of HLA-B. These associations correspond to the ancestral haplotype 8.1 and were not independent. Other positive associations from HLA-B and HLA-C were observed, such as serine (S) or tryptophan (W) at position 97 of HLA-B.

Subgroup 7 (anti-TIF1γ dominated), with all patients positive for anti-TIF1γ autoantibodies, had associations with HLA class II and I, including *HLA-DQA1*02*, *HLA-DQB1*05, HLA-DRB1*01*, and *HLA-DRB1*07* alleles, arginine (R) at position 71 of HLA-DRB1, threonine (T) at position 80 of HLA-B and phenylalanine (F) at position 9 of HLA-A.

Finally, subgroup 8 (negative for tested autoantibodies), had the highest median age at diagnosis with 58 years [IQR 46-68]. *HLA-DQA1*01*, *HLA-DQB1*06* and *HLA-DRB1*13* alleles, isoleucine (I) at position 95 and glutamic acid (E) at position 45 of HLA-B were positively associated with this subgroup.

Figure 14 | Amino acid associations
Manhattan-plot of the results of the imputed amino acid associations obtained from the meta-analyses of the UK and Scandinavian data. Subgroups are shown in columns and genes in rows. Selected amino acids with a FDR <0.01 are labelled, and the red line indicates the significance threshold for a 5% FDR. Panel A. Class II amino acid associations. Panel B. Class I amino acid associations. A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; S, serine; T, threonine; R, arginine; V, valine; W, tryptophan; Y, tyrosine.

5.2 Study II

→ **Based on the experience from a single center, it remains unclear if anti-ARS status is associated with a better clinical response to rituximab.**

Population

Sixty-five subjects with IIM exposed to ≥1 rituximab cycle were included in this study (**Figure 15**). Baseline characteristics of subjects included in the effectiveness analysis (n=43) are presented in **Table 10.** All patients in the anti-ARS group were classified as

anti-synthetase syndrome, while the anti-ARS negative group included 6 DM, 7 PM, 2 overlap myositis and 1 juvenile myositis. About half of the patients in each group were considered refractory (failed ≥2 immunosuppressors excluding corticosteroids). Comparable numbers of rituximab doses, cycles and cumulative doses were administered.

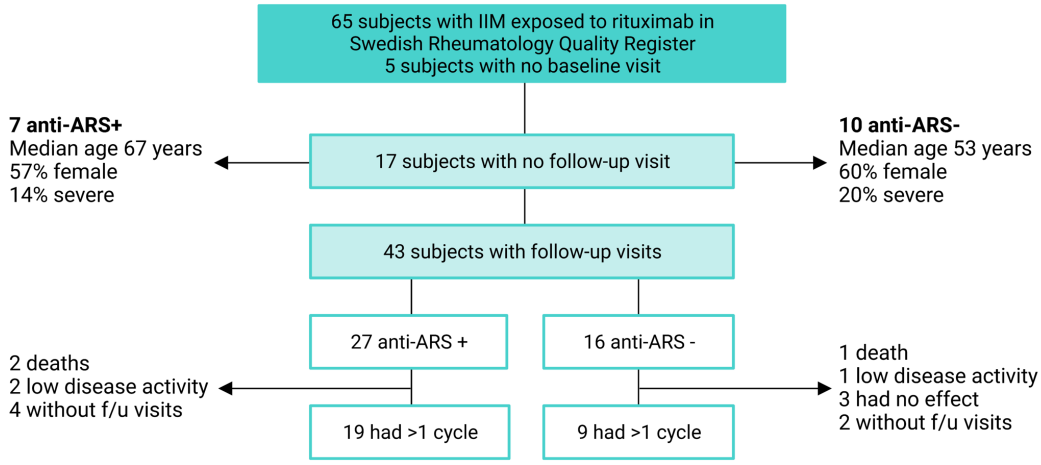


Figure 15 | Flow chart of patients included in the effectiveness analysis
In the anti-ARS positive group there were 21 anti-Jo1, 3 anti-PL7, and 3 anti-PL12. In the anti-ARS negative group there were 3 anti-TIF1y, 2 anti-MDA5, and 11 with no detectable MSA.
f/u, follow-up.

Table 10 | Baseline characteristics of the subject included in the effectiveness analysis

	Anti-ARS+ (n=27)	**Anti-ARS-** (n=16)
Female	19 (70)	11 (69)
Age (years), mean ± SD	57 ± 10	57 ± 19
Disease duration* (months), median [IQR]	**15 [4-52]**	**69 [9-166]**
Muscle weakness	**18 (67)**	**14 (88)**
ILD	**23 (85)**	**7 (44)**
DM rashes	3 (11)	6 (38)
Dysphagia	**5 (19)**	**10 (63)**
Severe disease	**17 (63)**	**3 (19)**
Previous treatment		
1 immunosuppressor	10 (37)	4 (25)
≥2 immunosuppressors	15 (56)	8 (50)
Reason for rituximab administration		
Multisystemic involvement	3 (11)	2 (13)
Refractory rash	1 (4)	2 (13)
ILD	**19 (70)**	**4 (25)**
Muscle weakness	4 (15)	4 (25)
Arthritis	**0**	**3 (19)**
Number of rituximab infusion, median [IQR]	4 [3-4]	4 [2-5]
Number of rituximab cycles, median [IQR]	3 [2-3]	2 [1-4]
Cumulative rituximab dose (g), median [IQR]	3.5 [3-4]	3.5 [2-5]

*Calculated from date of diagnosis. ILD, interstitial lung disease, DM, dermatomyositis.
n (%) if not otherwise specified. p <0.05 are shown in bold. Modified from Leclair et al.[255]

Seventeen IIM patients with baseline assessments were not included in the effectiveness analysis because of missing assessments in the time window where rituximab was expected to show a clinical effect (complete case analysis). Possible differences between patients excluded from the analysis and those included were explored. In the anti-ARS positive subgroup, the patients excluded were older (median age 67 vs 57 years, p=0.02) and tended to have less severe disease (14% vs 63%, p=0.06) but were similar in terms of clinical features, previous treatment failures and cumulative rituximab doses received. In the anti-ARS negative subgroup, no significant differences between patients included and excluded were found.

Effectiveness assessment

At baseline, the anti-ARS negative group was weaker and more functionally impaired compared to the anti-ARS positive group (**Table 11**). Mean time between first rituximab infusion and first effectiveness assessment was 7 months in the anti-ARS positive and 7.3 months in the anti-ARS negative groups. After the first rituximab cycle, anti-ARS positive and negative subjects had significantly improved their physician and extramuscular activity scores. Improvement in physical function and a significant decrease in median glucocorticoid doses was only seen in the anti-ARS positive group.

A moderate/major ACR/EULAR total improvement score was achieved in 78% of anti-ARS positive group compared to 50% in the anti-ARS negative group (p=0.12). Logistic regression analysis showed no association between anti-ARS status and moderate/major improvement after one cycle of rituximab, with an adjusted OR of 2.6 (95%CI 0.47-14.00, p-value 0.280).

Table 11. Effectiveness assessment after one rituximab cycle

	Baseline		After 1 cycle	
	Anti-ARS + n=27	**Anti-ARS –** n=16	**Anti-ARS +** n=27	**Anti-ARS –** n=16
VAS (0-100), mean ± SD				
Patient Global Activity	44 ± 28	59 ± 28	34 ± 23[a]	51 ± 26
Physician Global Activity	43 ± 17	41 ± 19	14 ± 14[a,b]	23 ± 10[b]
Extramuscular	37 ± 18	39 ± 21	10 ± 9[a,b]	21 ± 13[b]
HAQ	0.8 [0.3-1.3] [a]	1.7 [1.4-2]	0.4 [0-1][a,b]	1.5 [1-2]
MMT8	79 [73-80] [a]	74 [59-77]	79 [77-80]	77 [58-80]
CK levels	1.2 [0.8-8]	3.1 [1-26]	1.5 [0.9-2]	1.4 [0.7-3.8]
Glucocorticoid (mg)	20 [6-55]	11 [8-15]	10 [4-12.5][b]	11 [7.5-19]
ACR/EULAR improvement, n (%)				
Minimal improvement			21 (78)	12 (75)
Moderate improvement			21 (78)	8 (50)
Major improvement			10 (37)	4 (25)

Median [IQR] if not otherwise specified.

[a]Anti-ARS positive and negative comparison (p<0.05). [b]Anti-ARS defined groups baseline vs one cycle comparison (p<0.05).

VAS, visual analog scale; HAQ, Health Assessment Questionnaire; MMT, manual muscle testing; CK, creatine kinase. Modified from Leclair et al.[255]

In patients who received more than one rituximab cycle, both anti-ARS defined groups showed significant improvement in physician and extramuscular scores when compared to baseline. In comparison with the anti-ARS negative group, the anti-ARS positive group had sustained improvement in patient activity scores and functional disability measures. A significant glucocorticoid-sparing effect was only observed in the anti-ARS positive group with a median glucocorticoid dose decreasing from a baseline of 20mg [IQR 6-55] to 4mg [IQR 0-8] (p = 0.001).

Safety assessment

The safety assessment included 37 anti-ARS positive and 28 anti-ARS negative patients exposed to rituximab. During the follow-up period, infections were the most frequent adverse events in both groups with bacterial, viral, and opportunistic infections reported (**Figure 16**).

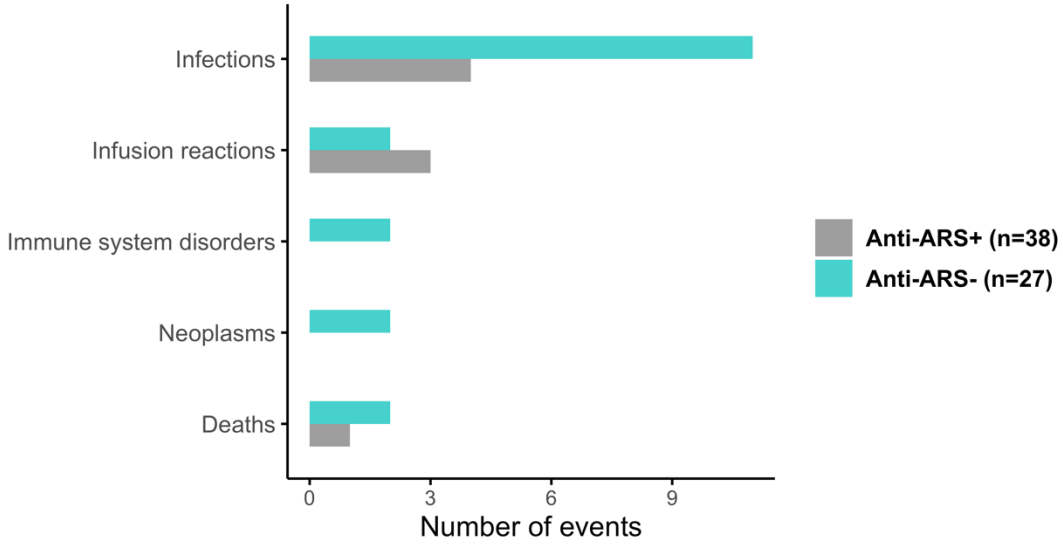


Figure 16 | Adverse events stratified by anti-ARS status
Two anti-ARS positive and one anti-ARS negative individuals died of pneumonia.

5.3 Study III

→ **IIM patients are at increased risk of ACS compared to the general population.**

Population

In **study III**, 655 incident IIM and 6813 matched general population comparators were included (**Table 12**). In the IIM group, 56% were women and 33% had DM. Numerical differences were noted in the prevalence of atrial fibrillation (IIM 6% vs general population 4%) and hypertension (IIM 13% vs general population 9%). Fifty-three ACS occurred in the IIM group compared to 313 in the general population. IIM patients experienced their first event earlier than the comparators (median 2.4 years [IQR 1.0–4.6] vs 3.5 years [IQR 1.8–6.0]).

Table 12 | Characteristics of the cohort

	IIM n=655	General population n=6813
Follow-up (years), median [IQR]	4.5 [2.5-8.0]	6.0 [3.4-8.9]
Female, n (%)	367 (56)	3821 (56)
Age (years), mean ± SD	60 ± 15	61 ± 15
Age group, n (%)		
<56 years	223 (34)	2242 (33)
56-67 years	215 (33)	2255 (33)
≥68 years	217 (33)	2316 (34)
Subsets, n (%)		
DM	218 (33)	
Other IIM	437 (67)	

DM, dermatomyositis; IIM, idiopathic inflammatory myopathies.
Modified from Leclair et al.[256]

Incidence rates and ACS risks

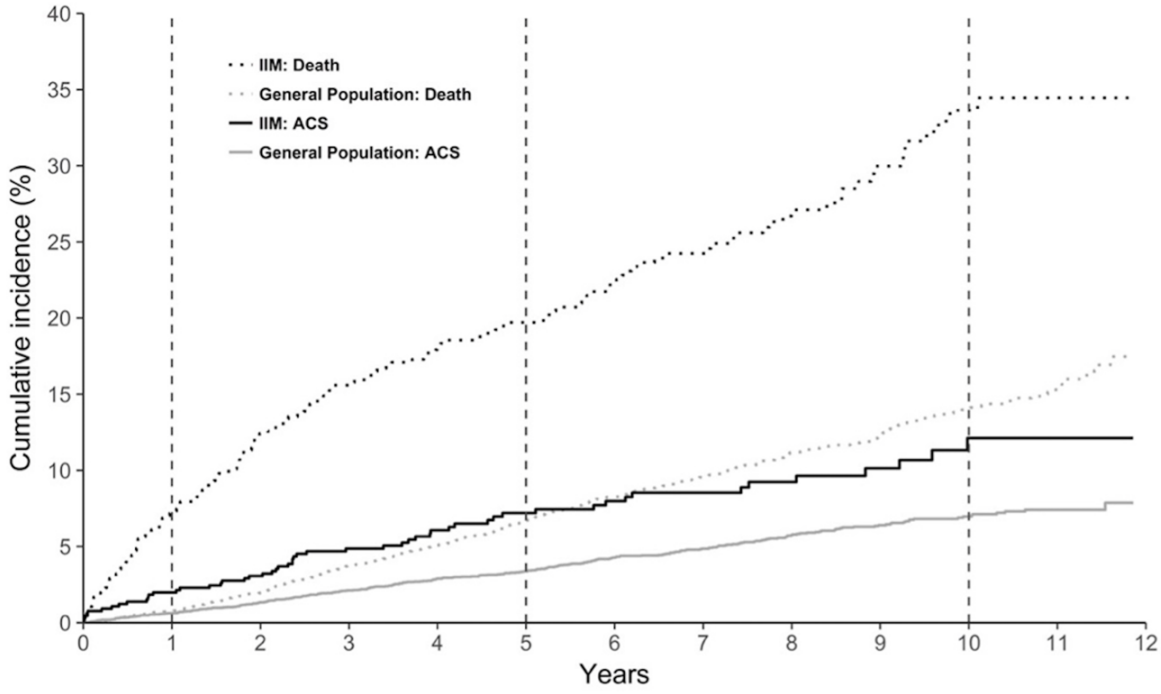
The unadjusted incidence rate for ACS in IIM was 15.6 (95%CI 11.7–20.4) per 1000 person-years compared to 7.5 (95%CI 6.7–8.4) in the general population (**Table 13**). In the IIM cohort, older individuals, and those with IIM other than DM had the highest ACS incidence rates. The adjusted HR for ACS comparing individuals with IIM and the general population was 2.4 (95%CI 1.8–3.2). When stratified by sex and age group, women had higher ACS risk than men and an increased risk was seen in the <56 and 68-90 age groups. When stratified by time since diagnosis, the risk of ACS was highest in the year following IIM diagnosis (HR 3.6 (95%CI 1.9–6.7)) and subsequently decreased (1-5 years HR 2.4 (95%CI 1.6-3.7); 5-12 years HR 1.8 (95%CI 1.0-3.3)).

Table 13 | Incidence rates and HR for ACS

	IIM Rate (95%CI)	General population Rate (95%CI)	HR (95%CI)
ACS	15.6 (11.7-20.4)	7.5 (6.7- 8.4)	2.4 (1.8-3.2)
Unstable angina	0.6 (0.1-2.1)	0.7 (0.4-1.0)	0.9 (0.2-3.7)
NSTEMI	5.0 (2.9-8.0)	2.5 (2.0-3.0)	2.3 (1.4-3.9)
STEMI	10 (6.9-14.0)	4.4 (3.7-5.0)	2.8 (1.9-4.0)
Sex			
Female	15.5 (10.5-22.1)	5.6 (4.7- 6.7)	3.4 (2.3-5.0)
Male	15.7 (9.9-23.5)	10.1 (8.6-11.7)	1.8 (1.2-2.8)
Age group			
<56 years	4.9 (2.0-10.1)	2.1 (1.5- 3.0)	2.4 (1.1-5.5)
56 – 67 years	9.6 (4.8-17.2)	6.1 (4.8- 7.5)	1.6 (0.8-3.0)
≥68 years	42 (29.2-58.4)	15.7 (13.6-18.1)	2.8 (2.0-4.1)
Subsets			
DM	7.5 (3.2-14.8)	6.3 (5.0-7.8)	1.2 (0.6-2.5)
Other IIM	19.3 (14.0-25.8)	8.1 (7.1-9.2)	2.5 (1.8-3.4)

Incidence rates per 1000 person-years.
NSTEMI, on ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; DM, dermatomyositis; IIM, idiopathic inflammatory myopathies.
Modified from Leclair et al.[256]

The overall sub-distribution HR for the association of IIM and ACS estimated by Fine and Gray competing risk models was 1.9 (95%CI 1.4–2.5). Competing risk models adjusted for age, sex, and place of residence were also used to estimate the cumulative incidence of ACS at 1, 5, and 10 years (**Figure 17**).



Cumulative incidence (%)	1 year	5 years	10 years
IIM patients	2	7.2	12.1
General population	0.6	3.4	7

Figure 17 | Cumulative incidence of ACS and death in IIM and general population comparators
Cumulative incidence of death depicted by the dotted lines and cumulative incidence of ACS by solid lines. Cumulative incidence of ACS estimated using Fine and Gray competing risk models.

5.4 Study IV

→ **There is a modification effect of cancer on the association between cancer and mortality in IIM.**

Population

In **study IV**, 230 adult patients with IIM diagnosed between 2004 and 2020 were included (**Table 14**). When comparing subjects unexposed or exposed to dysphagia, ILD was less frequent (25 vs 58%), with more DM (56 vs 28%) and less anti-synthetase syndrome (10 vs 36%) in the group exposed to dysphagia.

Table 14 | Baseline characteristics of the cohort stratified by dysphagia exposure

	No dysphagia n=118	**Dysphagia** n=112	**All** n=230
Age at diagnosis, *tertiles*			
<50 years	41 (35)	31 (28)	72 (31)
51-66 years	38 (32)	46 (41)	84 (37)
>66 years	39 (33)	35 (31)	74 (32)
Disease duration (months), mean ± SD	3 ± 2	3 ± 2	3 ± 2
Female	78 (66)	68 (61)	146 (64)
ILD	68 (58)	28 (25)	96 (42)
Arthritis	39 (33)	17 (15)	56 (24)
Raynaud phenomenon	21/111 (19)	19 (17)	40/223 (18)
Cardiac involvement	5/116 (4)	7/111 (6)	12/227 (5)
Proximal muscle weakness	98 (83)	106 (95)	204 (89)
Severe disease at baseline	61 (52)	61 (55)	122 (54)
Cancer	13 (11)	16 (14)	29 (13)
IVIg exposure	16 (14)	27 (24)	43 (19)
Subsets			
DM	33 (28)	63 (56)	96 (42)
Anti-synthetase	43 (36)	11 (10)	54 (24)
Overlap myositis	12 (10)	9 (8)	21 (9)
PM	27 (23)	25 (22)	52 (23)
IBM	3 (3)	4 (4)	7 (3)
Autoantibodies			
Anti-ARS	44 (37)	11 (10)	55 (24)
Anti-TIF1γ	10 (9)	18 (16)	28 (12)
Anti-NXP2	0	7 (6)	7 (3)
Anti-MDA5	10 (9)	5 (5)	15 (7)
Anti-SAE1	0	4 (4)	4 (2)
Anti-Mi2	6 (5)	7 (6)	13 (6)
Anti-SRP	1 (1)	6 (5)	7 (3)
Anti-HMGCR	7 (6)	4 (4)	11 (5)
No MSA	39 (33)	50 (45)	89 (39)
Anti-Ro52	33 (28)	12 (11)	45 (20)

n(%) if not otherwise specified.
ILD, interstitial lung disease; IVIg, intravenous immunoglobulins; DM, dermatomyositis; PM, polymyositis; IBM, inclusion body myositis; MSA, myositis-specific autoantibodies.

Mortality rates

The mortality rates per 100 person-year in the patients with IIM exposed to dysphagia was 5.0 (95%CI 3.0-7.8) compared to 3.0 (95%CI 1.5-5.4) in the unexposed group (**Table 15**). When considering dysphagia exposure based on cancer status, the mortality rates in the subjects without cancer were 2.1 (95%CI 0.9-4.3) in those unexposed to dysphagia and 2.3 (95%CI 1.0-4.5) in those exposed to dysphagia, while in the subjects with cancer the mortality rates were 11.9 (95%CI 3.2-30.4) in those unexposed to dysphagia and 33.3 (95%CI 16.6-59.5) in those exposed to dysphagia.

Table 15 | Mortality rates and risks associated with dysphagia

	n	P-Y	Mortality rates per 100 p-y	Crude HR (95%CI)	Stratified* HR (95%CI)
Dysphagia					
No	11	367	3.0 (1.5-5.4)	Reference	Reference
Yes	19	384	5.0 (3.0-7.8)	1.7 (0.8-3.6)	0.6 (0.2-1.5)
Cancer					
No	15	681	2.2 (1.2-3.6)	Reference	-
Yes	15	67	22.4 (12.6-37.0)	**9.4 (4.6-19.3)**	-
No dysphagia / no cancer	7	332	2.1 (0.9-4.3)	-	Reference
Dysphagia / no cancer	8	349	2.3 (1.0-4.5)	-	0.6 (0.2-1.8)
Dysphagia / cancer	-	-	-	-	**5.0 (1.0-24.6)**
No dysphagia / cancer	4	34	11.9 (3.2-30.4)	-	Reference
Dysphagia / cancer	11	33	33.3 (16.6-59.5)	-	2.9 (0.7-12.4)

n, number of deaths; P-Y, person-years.
*Model stratified on cancer status and adjusted for sex, age group at diagnosis, IIM subset including an interaction term between cancer and dysphagia. p <0.05 in bold.

Mortality risks

The crude HR for mortality in subjects exposed to dysphagia was 1.7 (95%CI 0.8-3.6). Crude Kaplan-Meier survival curves for individuals with IIM exposed and unexposed to dysphagia in early disease are shown in **Figure 18.A** and were not significantly different. Exposure to cancer was associated with the highest mortality risk with a crude HR of 9.4 (95% CI 4.6-19.3). Crude Kaplan-Meier survival curves for individuals with IIM exposed and unexposed to dysphagia stratified by cancer status were significantly different (p <0.0001, **Figure 18.B**).

Modification effect of cancer on the association between dysphagia and mortality

The stratified Cox proportional hazard model showed an adjusted HR for dysphagia exposure of 0.6 (95%CI 0.2-1.8) in the group without cancer and 2.9 (95%CI 0.7-12.4) in the group with cancer. Using the baseline rate of the patients with IIM without cancer unexposed to dysphagia as a reference, being exposed to cancer and dysphagia was associated with a HR of 5.0 (1.0-24.6) revealing a significant modification effect of cancer on the association between dysphagia and mortality.

The Cox proportional hazard models applied separately on subjects with and without cancer revealed similar adjusted HRs for dysphagia in the group without cancer of 0.6 (95%CI 0.2-1.5) compared to 2.8 (95%CI 0.9-8.9) in the cancer group. The results of the IPW-weighted stratified Cox proportional hazard model were also comparable to the adjusted stratified Cox proportional hazard model (**Figure 19**).

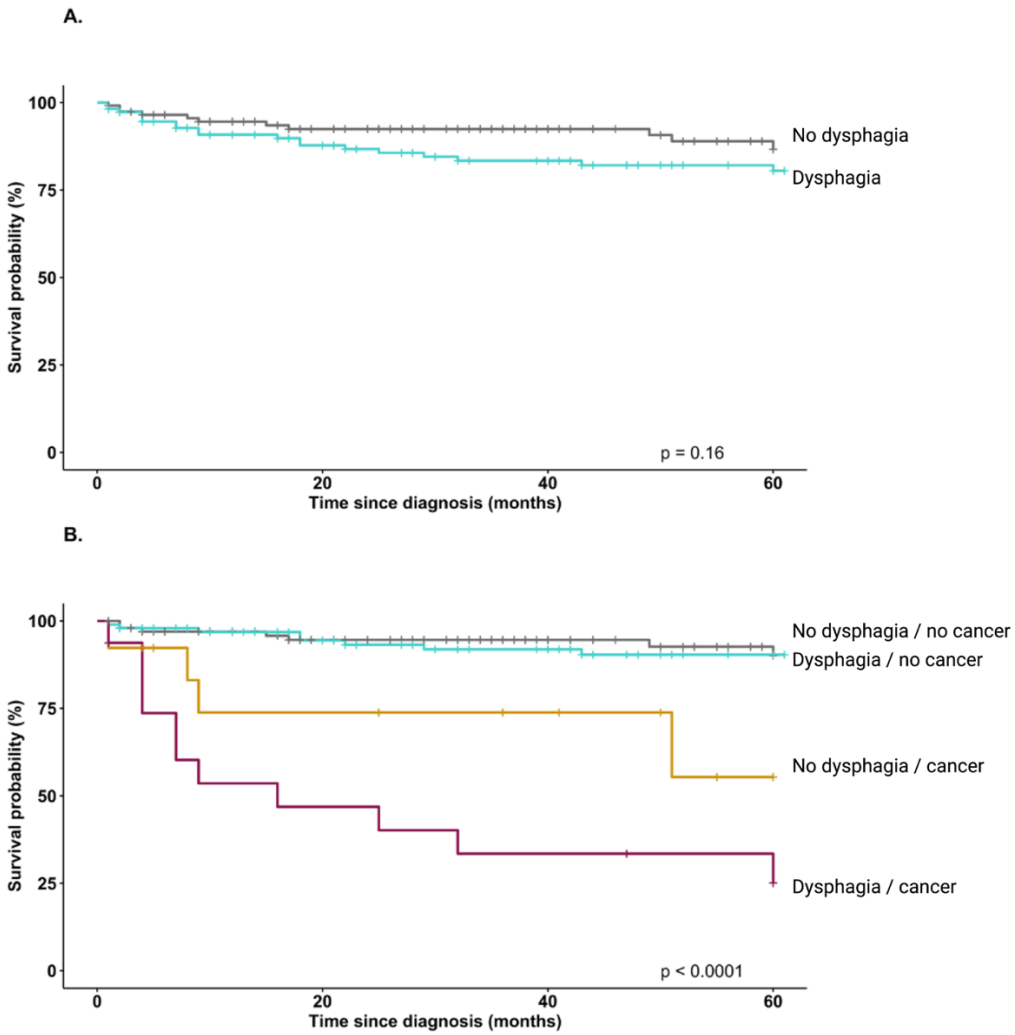


Figure 18 | Unadjusted survival curves

Panel A. depicts Kaplan-Meier curves for patients with IIM exposed or not to dysphagia in early disease. Panel B. depicts Kaplan-Meier curves for patients with IIM stratified by dysphagia and cancer status and demonstrates the differential effect of dysphagia exposure depending on cancer stratum. Differences between survival probabilities compared using the log rank test.

Models	Cancer	Hazard Ratio (95% CI)
Stratified Cox PH	**No**	0.6 (0.2-1.8)
Stratified Cox PH*	**Yes**	2.9 (0.7-12.4)
Separate Cox PH	**No**	0.6 (0.2-1.5)
Separate Cox PH*	**Yes**	2.8 (0.9-8.9)
IPW-weighted Cox PH	**No**	0.6 (0.2-2)
IPW-weighted Cox PH*	**Yes**	2.9 (0.6-13.4)

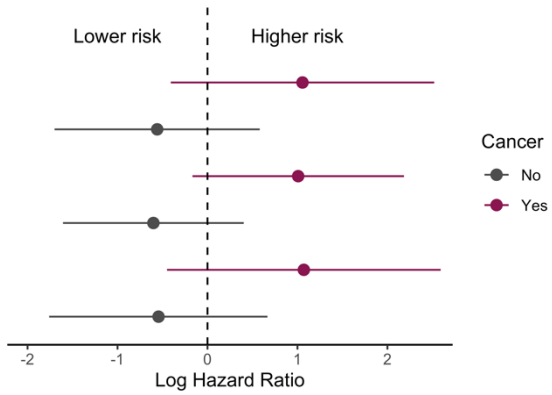


Figure 19 | Comparison of the models used to estimate the effect of dysphagia on mortality based on cancer exposure

Separate Cox models were applied on two separate datasets defined on cancer status and were adjusted for sex, age group at diagnosis, and IIM subset. The IPW-weighted Cox model corresponds to the stratified Cox model with adjustment for confounding using IPW.

PH, proportional hazard.

5.5 Study V

→ **Healthcare costs in IIM are 3 to 5-fold higher than the general population in the 5-year period following diagnosis.**

Population

In **study V**, 673 incident patients with IIM matched with 3343 general population comparators were included (**Table 16**). Of the patients with IIM, 16% were diagnosed with cancer ± 3 years from IIM diagnosis and 55% were of working age.

Table 16 | Characteristics of the cohort[257]

	All IIM n=673	IIM | Cancer n=111	IIM |Age <65 n=371	General population n=3343
Follow-up (years), mean ± SD	7.2 ± 1.5	6.4 ± 1.9	7.4 ± 1.2	7.5 ± 1.2
Female, n (%)	409 (61)	57 (51)	248 (67)	2040 (61)
Age (years), mean ± SD	60 ± 16	70 ± 11	49 ± 12	60 ± 16
Subsets, n (%)				
DM	265 (39)	61 (55)	166 (45)	
Other IIM	408 (61)	50 (45)	206 (55)	

IIM, idiopathic inflammatory myopathies; DM, dermatomyositis.

Healthcare costs

Mean ± SD healthcare costs started to increase two years before diagnosis reaching a maximum a year after diagnosis at €21639 ± 22733 compared to €4816 ± 10701 in the general population (**Table 17, Figure 20**). In IIM, outpatient visits, hospitalizations and productivity loss were the main drivers of these costs. In the year following diagnosis, direct costs accounted for 60% of total costs with mean (SD) costs for outpatient visits of €4099 ± 5147 and for inpatient care of €7003 ± 15168. While costs generally decreased in the following years, indirect costs related to disability pension increased.

Table 17 | Mean ± SD annual IIM healthcare costs (in €)[257]

		Hospital care		Productivity loss	
Year	Total	Outpatient	Inpatient	Disability pension	Sick leave
-5	4201±10257	682 ± 1800	512 ± 2209	2062 ± 7579	462 ± 2953
-4	4690±10542	766 ± 1998	549 ± 2118	1880 ± 7381	842 ± 3841
-3	4670 ± 10705	765 ± 1703	803 ± 3217	1709 ± 7166	780 ± 4002
-2	6027 ± 11414	1117 ± 2110	1134 ± 3720	1707 ± 6861	1334 ± 5501
-1	16818 ± 19106	3234 ± 3615	6490 ± 13221	1939 ± 7598	4052 ± 8360
+1	21639 ± 22733	4099 ± 5147	7003 ± 15168	2234 ± 8273	6716 ± 12241
+2	14622 ± 20908	2560 ± 3667	4207 ± 14406	2253 ± 8029	4177 ± 10073
+3	12209 ± 15848	2163 ± 2615	2769 ± 7010	3131 ± 9517	2603 ± 7035
+4	12936 ± 17998	2173 ± 3889	3041 ± 8301	3602 ± 10194	2111 ± 7108
+5	12796 ± 22092	1978 ± 3996	3671 ± 13826	3543 ± 10313	1830 ± 6571
General population					
+1	4816 ± 10701	740 ± 1877	1153 ± 4568	1700 ± 7337	779 ± 4068

Overall mean total annual IIM costs were higher in women, in the working age group and in patients with cancer (**Figure 20.B**). In the year following diagnosis, the mean annual ± SD cost in the cancer-associated group was €28612 ± 25624, with hospital care representing 74% of these costs.

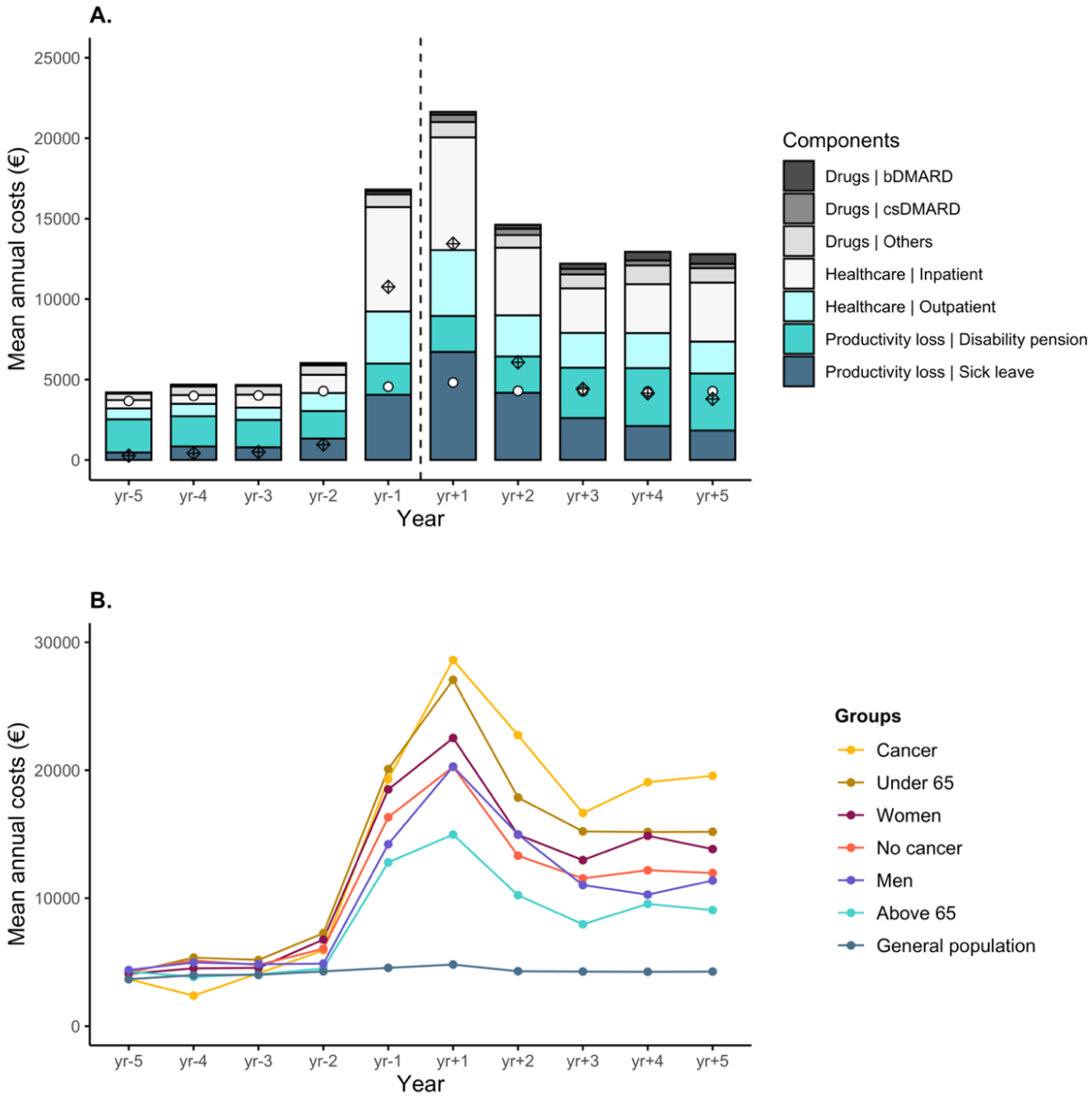


Figure 20 | Annual IIM healthcare costs (in €)
Panel A. Mean annual costs are represented by the bars, median costs by the crossed circles and mean total costs for the general population by the circles. Panel B. Mean annual costs stratified by age group, sex, and cancer status. bDMARD, biologic disease modifying anti-rheumatic drugs, csDMARD, conventional synthetic disease modifying anti-rheumatic drugs.
Panel A was adapted with permission from Elsevier: *Seminars in Arthritis and Rheumatism*, "Distribution and trajectory of direct and indirect costs of idiopathic inflammatory myopathies" by Leclair V, Moshtaghi-Svensson J, Hudson M, et al. Copyright 2021.

6 Discussion

Allowing for their strengths and limitations, the different studies included in this thesis contribute to the existing literature in several ways.

6.1 Leveraging existing databases

Different data sources were used to address the many questions motivating the projects included in this thesis. In IIM, clinical registries are extremely important as they not only contain patient-level data on clinical phenotypes and disease activity measures, but also autoantibody serologies. In **study I**, access to such information allowed the detection of distinct associations between autoantibody-defined subgroups and HLA variants in IIM. This project required a large number of patients with IIM with well-defined serologies and HLA genotyping, and was only possible through a multicenter international collaboration, although this introduced some heterogeneity in the clinical data collected. In **study II**, where both serological data, and detailed longitudinal drug exposure data were necessary, a single center clinical registry was used. While very complete longitudinal data on IIM patients exposed to rituximab could be retrieved from the Swedish Rheumatology Quality Register, it resulted in a small sample size with ensuing power issues and methodological limitations. Similarly, in **study IV**, for ascertainment of dysphagia exposure in early disease, careful clinical data at onset that could only be accessed through clinical registries was necessary. This again resulted in some power issues but allowed for the demonstration of a clear modification effect of cancer on the association between dysphagia in early disease and mortality in IIM. Clinical registries are thus of fundamental importance for clinical research in IIM, but are limited in size, and lack data harmonization between centers.

Population-based studies offer the advantage of larger sample sizes of cases, access to general population comparators and the possibility of linkage to multiple administrative databases. This approach is particularly powerful for study questions that aim to inform policy makers or researchers on areas to prioritize for resource allocation or future research. In **study III**, this approach demonstrated that IIM patients are at increased risk of ACS compared to the general population. In this case, the use of administrative databases increased the detection of the outcome while decreasing the risk of misclassification as reliable case definitions were available for identification of cardiovascular risk factors, ACS, and death. Moreover, in **study V**, this linkage generated the first Swedish estimates of direct and indirect healthcare costs for IIM compared to the general population. Still, given the heterogeneity of the IIM population identified through ICD codes, generalization remains challenging and further studies are needed to understand the explanatory mechanisms behind these findings.

6.2 Leaving no autoantibodies behind

Autoantibodies are useful for delineating more homogeneous IIM subsets and, in certain settings, are helpful for prognostication. Previous studies showed distinct HLA alleles associations with individual autoantibody found in IIM[44,116,119–127]. However, the reality is more complex and IIM patients often have combinations of MSA and MAA. The outcomes associated with these combinations are not well-defined, but in some instances may be associated with worse prognosis, such as in patients with anti-Jo1 who are also positive for anti-Ro52[151,193,194]. In line with these clinical observations, differential genetic associations for HLA class I between isolated anti-Jo1 and anti-Jo1 in combination with anti-Ro52 autoantibodies were found in **study I**. The subgroup dominated by anti-Jo1/Ro52 showed three signals from HLA-B amino acids, two of which were not found in the subgroup dominated only by anti-Jo1 autoantibodies and that appear to be independent from the haplotype 8.1. These findings suggest that different pathophysiological mechanisms are responsible for the production of multiple autoantibodies in a same patient with IIM (e.g., anti-Jo1 and anti-Ro52) where cell apoptosis in inflamed or damaged tissue (e.g., muscle, skin, lung) could lead to a loss of peripheral tolerance, generation of autoreactive T-cells and co-occurrence of autoantibodies as illustrated in **Figure 21**[258–261].

IIM subgrouping based on autoantibody profiles may then reflect distinct pathogenetic mechanisms better than subgrouping using traditional classification approaches based on clinical and histopathological features. In antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, distinct genetic predispositions are found depending on ANCA specificity suggesting that proteinase 3 ANCA and myeloperoxidase ANCA-associated vasculitis are distinct syndromes[262]. Moreover, in ANCA vasculitis and rheumatoid arthritis the presence of some HLA alleles are associated with clinical response to treatment[263–265]. Considering specific HLA alleles as possible response predictors in outcome research or drug effectiveness trials could potentially help personalize treatment decision in IIM. Likewise, integration of autoantibody profiles in IIM classification, a central component of clinical and translational research, could be instrumental to find targeted therapies for patients with IIM. The integration of autoantibodies in classification criteria has been advocated by researchers in the past, and our results support this approach as they suggest distinct genetic susceptibility based on autoantibody profiles[266,267].

6.3 Bridging the therapeutic gap

Given the rarity and heterogeneity of IIM, it is challenging to conduct clinical trials in these diseases, resulting in a paucity of evidence to guide clinicians in their therapeutic decisions. Effectiveness trials measure the degree of beneficial effect in routine clinical settings and is an attractive alternative in the absence of randomized controlled trials.

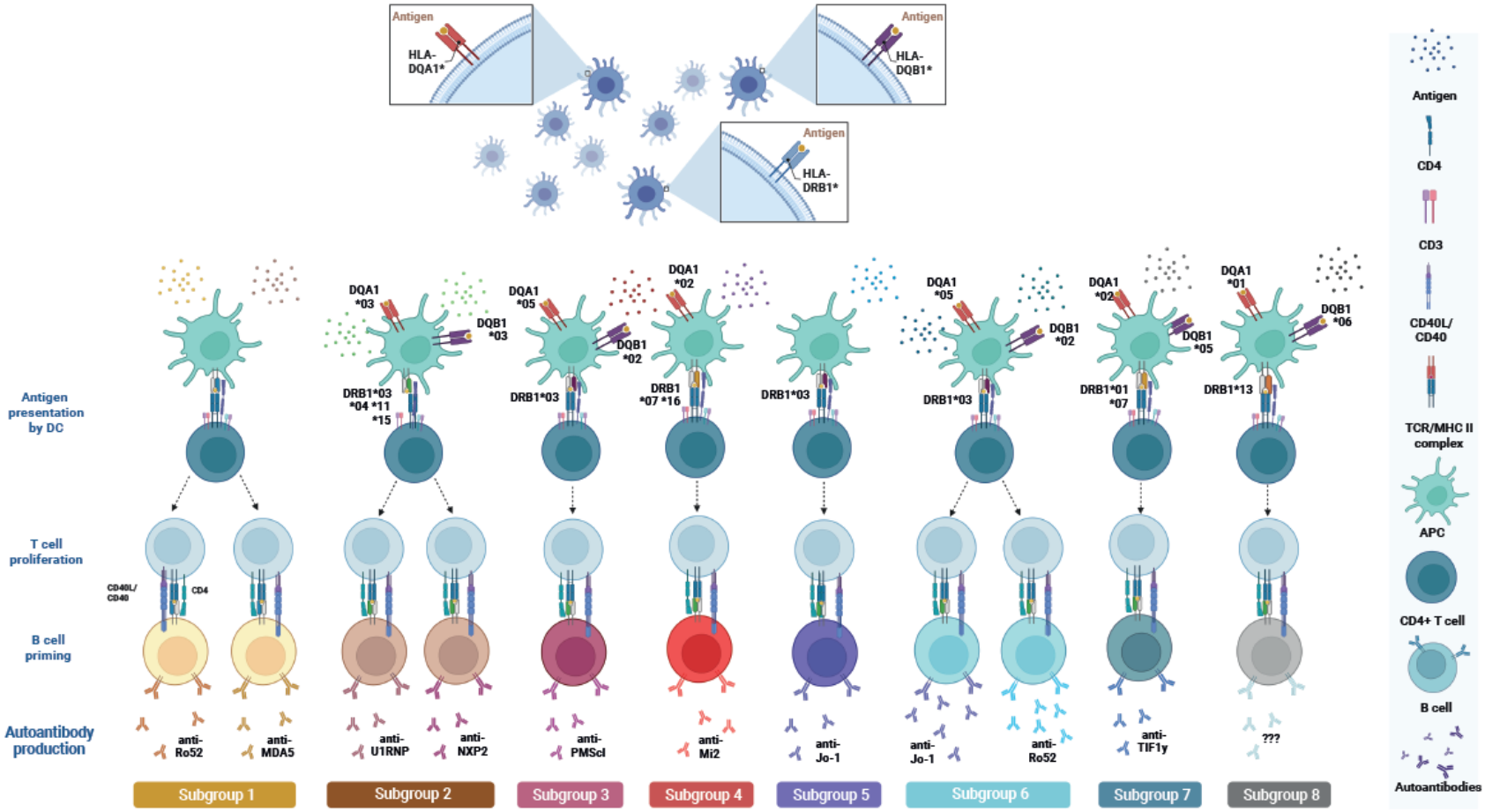


Figure 21 | Suggested mechanisms for the production of autoantibody specific and associated with IIM

Different HLA molecules, genetically determined, influence antigen presentation, T-cell differentiation and proliferation, and B-cell priming, leading to specific autoantibody production in IIM. Based on the expression of HLA alleles, distinct autoantibodies are produced. In some cases, like in subgroup 1 or 6, this differential expression of MHCII would lead to B-cell priming and production of both MSA (e.g., anti-Jo1 or anti-MDA5) and MAA (e.g., anti-Ro52) in the same individual.

DC, dendritic cells; TCR, T-cell receptor; APC, antigen presenting cell. Created with BioRender.

In **study II**, the effectiveness of rituximab was compared between anti-ARS positive and negative patients. At the time this study was conducted, comparative effectiveness of rituximab in IIM based on autoantibody status had never been explored. The decision to compare effectiveness based on anti-ARS status was guided by the post-hoc analyses of the RIM trial, and observational studies reporting good clinical response in anti-synthetase syndrome[145-151,153,155,268]. Although only anti-ARS positive patients improved their physical function after one cycle of rituximab, there was no significant difference in the proportion of patients that achieved a moderate to major ACR/EULAR improvement score.

Some methodological aspects could however explain this lack of difference. First, the study design was at risk of attrition bias as only patients with a study visit for clinical response assessment were kept for the effectiveness analyses (complete case analysis). When systematic differences exist between patients who are lost to follow-up and those who remain in a study, an attrition bias can be introduced[269]. In **study II**, when patients excluded for lack of follow-up were compared to those included in the analysis, differences were found in the anti-ARS positive subgroup where older and less severe patients were excluded from the analysis. If those patients were lost to follow-up because they had a good response to rituximab, this might have biased the results towards the null. Moreover, the small sample size limited statistical modeling and the use of bias reduction methods such as multiple imputation or IPW[270,271]. Nonetheless, of patients analyzed in **study II**, 21/27 (78%) of anti-ARS positive patients and 8/16 (50%) of anti-ARS negative patients achieved a moderate/major ACR/EULAR total improvement score after one cycle, which suggests effectiveness of the treatment in routine clinical practice with an overall favorable safety profile.

Large international clinical registries with longitudinal data on treatment and activity measures should be encouraged to allow researchers to conduct comparative effectiveness studies in IIM with robust methodology to account for possible confounding and attrition bias[272]. This could help bridge the therapeutic gap in IIM but would require high quality data, standardized techniques for autoantibody detection and reliable outcome measures for clinical response definitions.

6.4 Taking a closer look at cardiovascular risk

Previous estimates of ACS risk in IIM using administrative databases showed increased ACS risk in DM and PM compared to the general population[181,273,274]. Based on the National Health Insurance in Taiwan, an adjusted HR for ACS of 1.98 (95%CI 1.17-3.35) was found in PM/DM[273]. Later, based on the same data source, differences in ACS risk between DM and PM patients were found with a higher adjusted HR in PM of 3.7 (95%CI 2.8-4.9) compared to DM with 2.2 (95% CI 1.6-3.0) [274]. Similarly, a Canadian population-based study found an adjusted HR for ACS in PM of 5.2 (95%CI 3.3-8.2) compared to 3.5 (95%CI 1.9- 6.5) in DM[181].

In **study III**, an overall adjusted HR for ACS of 2.4 (2.2-9.3) was found, but in contrast with previous studies, this increased risk remained significant only in the "other IIM" subgroup including patients with PM, anti-synthetase, overlap myositis and IBM . Although the case and outcome definitions used were similar to previous reports, the sample size for DM in **study III** was smaller and only eight ACS events were captured during the follow-up period, likely indicating a power issue.

ACS risks in survival studies are often estimated using standard Cox proportional hazard models. Still, this type of modelling was shown to overestimate the risk of coronary heart disease in frail populations[275]. The use of a competing risk analysis in **study III** addressed that issue and confirmed the association between IIM exposure and an increased incidence of ACS compared to the general population. This potential source of bias was never considered in previous studies[181,273,274]. In time-to-event analyses in IIM, competing risk should always be considered when the outcome of interest is not all-cause mortality, as high mortality rates in that population could bias risk estimates.

Of note, novel sex differences in ACS risks were found in **study III**. While females and males had similar ACS incidence rates (16/1000 person-year) in the IIM group, when analyses were stratified on sex, higher adjusted HR for ACS were found in females compared to males. The mechanisms behind these differences have not been studied in IIM but could potentially be explained by a loss of the cardioprotective effect of female hormones in IIM secondary to persistent inflammation and/or immunosuppressive treatment[276]. Moreover, previous studies in rheumatoid arthritis showed significant underestimation of cardiovascular risk in females when using cardiovascular risk calculators[277]. Still, current EULAR guidelines for cardiovascular risk management in IIM recommend cardiovascular risk factors assessment using standard prediction tools, which is concerning especially since ACS risk estimates in females with IIM are higher than in rheumatoid arthritis[278,279]. Our findings thus not only confirm an increased ACS risk in patients with IIM, but also shed light on important sex differences in cardiovascular risk in IIM. The lack of systematic sex stratification in outcome research is a barrier to understand the possible differential mechanisms of increased cardiovascular risk in females and males. Aside from known biological differences between females and males, considering sex differences could avoid incorrect inferences with possible damaging interventions and should be standard practice[280].

6.5 Making sense of conflicting results

Conflicting results are frequent in the medical literature, a reflection to some extent of methodological and reporting issues[281]. Outcome research in IIM is particularly prone to methodological challenges with small sample sizes and several possible sources of confounding and bias. Reports on the association between dysphagia and mortality are scarce with early studies suggesting an increased mortality risk in IIM based on crude

estimates[195,196]. In later studies that addressed possible confounding by adjusting notably for age and cancer, this association however disappeared[203]. The conclusion that might be drawn from this literature could be that there is in fact no association between dysphagia and mortality in IIM, ignoring the possibility that cancer could be a modifier of this relationship and not a confounder. In **study IV**, the unadjusted survival curves stratified by dysphagia and cancer status clearly indicate that the effect of dysphagia is different depending on cancer status (**Figure 18.B**). Furthermore, a Cox proportional hazard model stratified on cancer status showed adjusted HR for dysphagia exposure going in opposite directions with a significant interaction between dysphagia and cancer suggesting that there is a modification effect of cancer on the association between dysphagia and mortality.

In that context, can IIM patients with and without cancer be analyzed together when the outcome of interest is mortality? When the adjusted Cox proportional hazard models were applied on IIM patients with and without cancer separately, the effect of other covariates on mortality risks were also different (e.g., age) indicating that patients with IIM and cancer are different than those without cancer. In **study IV**, cancer had a low prevalence (13%), while in the larger group unexposed to cancer, mortality rate was very low (2.2 per 100 person-year). Consequently, for a significant number of patients to experience the outcome of interest (i.e., death) in the no cancer and cancer strata, a much larger number of patients would be required. To estimate the definitive effect of dysphagia on mortality, large international collaborations will be necessary as the findings of **study IV** are suggesting that IIM patients with and without cancer cannot be analyzed together when the outcome of interest is mortality.

Various mechanisms could explain the differential effects of dysphagia in the presence or absence of cancer. First, dysphagia mechanisms could differ in patients with or without cancer. In IIM, oropharyngeal dysphagia is thought to be secondary to local myositis potentially reversible with immunosuppression[38-41]. In cancer, dysphagia can result from mechanical obstruction by the tumor or sequelae from surgery or radiation. Other factors associated to the cancer and its treatment such as oral ulcers, xerostomia, fatigue, pain, nausea, vomiting, sarcopenia and psychological stress can also affect swallowing functions[282]. In addition, cancer patients are often exposed to highly immunosuppressive regimens compared to standard IIM treatments exposing them to higher risk of infectious complications, including aspiration pneumonias. Finally, in certain cases, interactions between IIM regimens and chemotherapy or poor tolerance of dual treatment of those conditions can lead to suboptimal management[283]. Future studies are needed to understand the mechanisms and optimal management of dysphagia in cancer-associated IIM as these patients face high mortality risks.

6.6 Uncovering the hidden costs of IIM

Healthcare costs are essential to better understand the burden of a condition, guide policy makers and highlight areas of need for quality-of-care improvement. In **study V**, overall healthcare costs of IIM were estimated in Sweden for the first time with a mean annual cost in the year following diagnosis at €21639 compared to €4816 in the general population. These cost estimates are similar or higher than those reported in systemic lupus erythematosus with <5 years duration (€19920), and rheumatoid arthritis in the year following diagnosis (€12372)[214,284]. Our direct costs estimates were similar to those found using insurance data claims in a US IIM incident cohort and higher than those reported in a prevalent IIM Canadian cohort[205,207]. Although some studies had previously reported on productivity loss in IIM in terms of days or percentage of work time lost, **study V** provided the first estimates of indirect costs in IIM[210,285-287].

The fact that costs were at their highest in the years prior to and after diagnosis is expected as it corresponds to a period when patients have active disease and are exposed to multiple investigations to diagnose and stage their disease, and to screen for cancer and comorbidities. However, what is often forgotten and highlighted in **study V** is that during the same period, patients experience substantial productivity loss resulting in significant indirect costs. Our estimates showed that, beyond this period, indirect costs account for 40 to 60% of overall healthcare expenditures in IIM. Long-term productivity loss was particularly noted in women, which is representative of the well-documented gender gap in sick leaves that affects women more than men in many countries[288]. The exact reasons behind this gender gap remain unclear but could be related to differential familial workload, working environments and work-related attitudes towards absenteeism between women and men[289].

The year following diagnosis seems to be a pivotal period for improving clinical outcomes in IIM. As shown in **studies III** and **IV**, it is a period when patients with IIM are at increased risk of morbidity and mortality and thus represent a window of opportunity for impactful interventions. Early intensive immunosuppression is associated with better outcomes at one year and decreased number of flares are associated with less functional disability and increased work ability supporting that early and sustained remission are beneficial[285,290]. Addressing potentially preventable comorbidities such as cardiovascular diseases and infections could thus improve quality-of-care in IIM and potentially reduce short-term and long-term healthcare costs. Finally, a priority for future research is to develop better algorithms for cancer screening in IIM and understand how to optimally manage both the IIM and the cancer, as this subgroup experiences the worse outcomes within the IIM spectrum.

7 Conclusions & future directions

Despite many advances in the field, there is still significant morbidity and mortality in IIM. As discussed throughout this thesis, there are many challenges to conduct outcome research in IIM due notably to the rarity and heterogeneity of the condition. The different studies included herein serve to advance our knowledge on clinical outcomes in IIM and provide important insight to improve the design of future projects in the field (**Figure 22**).

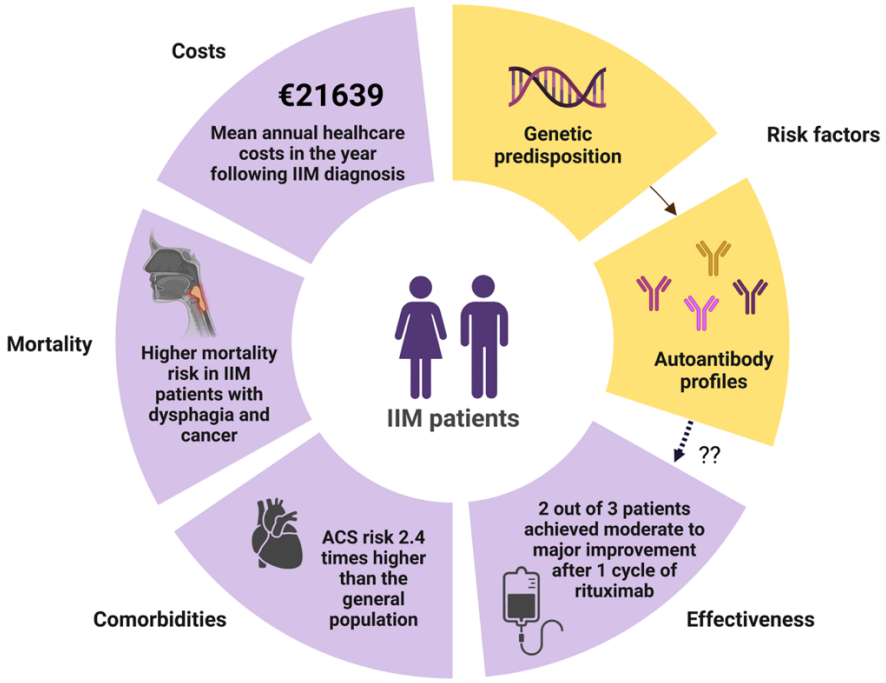


Figure 22 | Overview of the findings from the different projects
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The results of **study I** support the incorporation of autoantibody profiles in IIM classification with the demonstration of distinct HLA class II and I associations with autoantibody-defined IIM subgroups. An IIM classification scheme reflective of pathogenic mechanisms has not yet been adopted and would be important to better understand the role of the adaptive immune system in IIM. This could perhaps lead to better prediction of clinical outcomes and treatment response, although this needs to be further studied.

In **study II**, anti-ARS status was used to compare rituximab effectiveness, and despite the risk of bias and small sample size, significant improvement in patient-reported outcomes were found in anti-tRNA synthetase positive patients but not in anti-tRNA synthetase negative patients. Moreover, 67% of the patients included achieved moderate/major ACR/EULAR improvement supporting the effectiveness of rituximab in IIM. Larger multicenter studies with detailed harmonized clinical phenotyping and longitudinal data

are needed to conduct robust comparative effectiveness studies in IIM to help guide IIM management in practice.

The findings of **study III** highlight the substantial increase in ACS risk in IIM which was 2.4-fold higher than in the general population. Moreover, stratified estimates showed a 3.4-fold increase in ACS risk in females compared to the general population which was higher than in males who had a 1.8-fold increase. These findings underline important sex differences in cardiovascular risk in IIM that could result notably from underestimation of cardiovascular risk in females when using current suggested cardiovascular risk calculators. Further studies aimed at understanding the mechanisms leading to higher cardiovascular risks in IIM and identifying potential interventions to reduce cardiovascular morbidity in that population are urgently needed.

In **study IV**, a modification effect of cancer on the association between dysphagia in early disease and mortality was demonstrated, with dual exposure to dysphagia and cancer associated with a 5-fold higher mortality risk using patients unexposed to cancer and dysphagia as a reference. Our results emphasize the important differences between non-cancer and cancer patients affected by IIM that might preclude their combination in future survival analyses, at least when the outcome is mortality. Although this might create an issue for outcome research in cancer-associated IIM, it would reduce the risk of modification effect that could distort estimates.

Finally in **study V,** direct and indirect annual healthcare costs of IIM in Sweden were estimated for the first time and were found to be 3 to 5-fold higher than in the general population in the 5-year period following diagnosis. Indirect costs (i.e., productivity loss), which are often forgotten by clinicians and researchers, accounted for 40% to 60% of these costs. These estimates are important for researchers as they reflect the important societal burden of the disease and can help raise awareness and secure resources to address unmet needs in IIM. Future research in IIM should focus on understanding what interventions could mitigate these costs while improving clinical care.

In summary, the findings reported in this thesis support a shift in IIM classification with the inclusion of autoantibody profiles reflective of underlying pathogenic mechanisms and propose that bridging the therapeutic gap, reducing the cardiovascular comorbidities, improving cancer-associated screening and management, and exploring determinants of direct and indirect healthcare costs could improve clinical outcomes in IIM. However, to achieve such goals in rare and complex diseases such as IIM, it is important to leverage all existing data sources and collaborate on international longitudinal registries using harmonized definitions, detailed serologies and validated outcomes measures.

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