Cardiac involvement in idiopathic inflammatory myopathies

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“It is only with the heart one can see rightly; what is essential is invisible to the eye”

Antoine de Saint-Exupéry, *The Little Prince*

To Samir, Sara, Nora and Natalia

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ABSTRACT

Idiopathic inflammatory myopathies (IIM) are a group of autoimmune systemic rheumatic diseases characterized by skeletal muscle inflammation and extramuscular organ involvement. The heart is one of the organs that can be affected by IIM. Cardiac manifestations, including myocarditis occur often at disease onset and subsequent cardiovascular comorbidities in IIM have been recognized as major contributors to mortality in IIM. However, detecting the cardiac involvement in IIM remains challenging for rheumatologists. Clear guidelines for identifying cardiac involvement are lacking, and routine cardiac screening is not currently part of standard care of IIM.

This thesis aimed to verify the prevalence of myocardial inflammation and cardiovascular comorbidities in IIM. Furthermore, we sought to identify the practical and reliable assessment tools for the early detection the cardiac involvement in IIM. To achieve our goals, we utilized two IIM patient cohorts: a cross-sectional cohort and a prospective cohort.

Our cross-sectional study demonstrated a higher prevalence of traditional cardiovascular risk factors, electrocardiographic and echocardiographic abnormalities among IIM patients along with elevated levels of cardiac

biomarkers. Prospective cohort data revealed that, at disease onset, 47% of IIM patients had cardiac structural abnormalities detected by cardiac magnetic resonance (CMR), indicative of cardiac involvement in IIM. Cardiac involvement was closely associated with the severity of skeletal muscle involvement. Furthermore, we identified soluble suppression of tumorigenicity 2 as a potential biomarker for early detection and monitoring of cardiac involvement in IIM. We also found that cardiac inflammation appeared to respond favourably to treatment with corticosteroids and other immunosuppressive therapies. However, myocardial fibrosis was still a frequent finding at 24-month follow-up.

In conclusion, patients with IIM are at increased risk of both traditional cardiovascular comorbidities and myocardial inflammation. A standardized screening protocols incorporating cardiac biomarkers and CMR may facilitate the early detection of the cardiac involvement in IIM. Such an approach could improve risk stratification, guide targeted therapeutic interventions and ultimately enhance clinical outcomes while reducing cardiovascular morbidity and mortality.

Keywords: Idiopathic inflammatory myopathies, cardiovascular diseases, diagnostic tools.

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SAMMANFATTNING PÅ SVENSKA

Idiopatiska inflammatoriska myopatier (IIM) är en grupp av autoimmuna systemiska reumatiska sjukdomar som kännetecknas av skelettmuskelinflammation och engagemang av extramuskulära organ. Hjärtat är ett av de organ som kan påverkas vid IIM. Hjärtengagemang, såsom myokardit (hjärtmuskelinflammation), perikardit (hjärtsäcksinflammation), arytmier (oregelbunden hjärtrytm) och kardiovaskulära samsjukligheter vid IIM, har nyligen identifierats som en av de viktigaste orsakerna till mortalitet vid IIM. Hjärtengagemang har studerats vid IIM, men i mindre utsträckning än vid flera andra reumatiska sjukdomar. Att verifiera hjärtengagemang vid IIM är fortfarande en stor utmaning för reumatologer, eftersom tydliga riktlinjer för att upptäcka hjärtpåverkan saknas och screening av hjärtengagemang för närvarande inte ingår rutinmässigt i standardvården av patienter med IIM.

Denna avhandling syftar till att fastställa prevalensen av hjärtengagemang och kardiovaskulära samsjukligheter vid IIM. Vidare syftar avhandlingen till att identifiera de mest användbara undersökningsmetoderna för att upptäcka hjärtavvikelser tidigt och på ett enkelt sätt vid IIM. För att uppnå dessa mål användes två patientkohorter: en tvärsnittskohort och en prospektiv kohort.

I **delarbete I** visade vi att patienter med IIM har en högre prevalens av traditionella kardiovaskulära riskfaktorer, såsom obesitas, diabetes mellitus och dyslipidemi, patologiska elektrokardiografiska förändringar samt förhöjda markörer för hjärtskada jämfört med friska kontroller. I **delarbete II** visade vi att hjärtengagemang är vanligt förekommande vid sjukdomsdebut hos patienter med IIM och att det är nära associerat med graden av skelettmuskelengagemang. I **delarbete III** undersöktes den potentiella användbarheten av soluble suppression of tumorigenicity 2 (sST2) som biomarkör för tidig upptäckt och uppföljning av hjärtengagemang vid IIM. I

delarbete IV rapporterade vi resultat från långtidsuppföljning av patienter med IIM och visade en tydlig förbättring av sjukdomsaktivitet och hjärtmarkörer, medan hjärtmuskelfibros kvarstod ofta. Svår hjärtpåverkan var kopplad till fortsatt förhöjda hjärtmarkörer och nedsatt hjärtfunktion.

Sammanfattningsvis har patienter med IIM en ökad risk för traditionella kardiovaskulära samsjukligheter samt inflammation i hjärtmuskeln. Dessa resultat understryker behovet av att etablera standardiserade och systematiska protokoll för tidig upptäckt och handläggning av hjärtengagemang vid IIM, i syfte att förbättra riskstratifiering, vägleda riktade terapeutiska interventioner och i slutändan förbättra kliniska utfall samt minska kardiovaskulär sjuklighet och dödlighet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Hanna B**, Polte C L, Sakiniene E, Brömsen J V, Bollano E, Pullerits R, Jin T. Cardiovascular risk and cardiac involvement in idiopathic inflammatory myopathies: insights from a cross-sectional Swedish single-centre study. Scand J Rheumatol 2025; 54 (4): 272-281.

II. **Hanna B**, Polte C L, Sakiniene E, Brömsen J V, Bollano E, Lundberg I E, Pullerits R, Jin T. Cardiac involvement in newly diagnosed patients with idiopathic inflammatory myopathies is associated with skeletal muscle involvement. Clin Exp Rheumatol 2026; 44 (2): 320-329.

III. **Hanna B**, Lundberg I E, Ekwall A-K H, Glinatsi D, Sakiniene E, Hu Z, Pullerits R, Jin T. Elevated sST2 associates with cardiac involvement and declines after treatment in newly diagnosed patients with idiopathic inflammatory myopathies. Arthritis Res Ther 2026; 19;28(1):109.

IV. **Hanna B**, Polte C L, Sakiniene E, Gjertsson I, Brömsen J V, Aziz S, Pullerits R, Jin T. Evolution of cardiac involvement in idiopathic inflammatory myopathies: A 24-month prospective follow-up study. Manuscript submitted.

LIST OF PAPERS NOT INCLUDED IN THE THESIS

1. Svensson J, Holmqvist M, Tjärnlund A, Dastmalchi M, **Hanna B**, Magnusson Bucher S, Lundberg IE. Use of biologic agents in idiopathic inflammatory myopathies in Sweden: a descriptive study of real life treatment. Clin Exp Rheumatol 2017:35(3):512-515.

2. **Hanna B**, Sakiniene E, Gjertsson I, Pullerits R, Jin T. Osteopenia/osteoporosis develops in the early phase of disease in patients with idiopayhic inflammatory myopathies. Scand J Rheumatol 2021:50(5):398-401.

3. Polte CL, Bergh N, Oldfors A, **Hanna B**, Bollano E. Cardiac involvement in immune-mediated necrotizing myopathy: Insight from CMR and somatostatin receptor PET/CT. Eur Heart J Cardiovasc Imaging 2022:23(5):e237.

4. Marklund J, **Hanna B**, Jin T, Pullerits R. Myositis-associated antibodies predict the severity of lung involvement in adult patients with inflammatory myositis – a cohort study of 70 adult patients with myositis in a single center. Front Med (Lausanne) 2024: 11: 1340310.

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ABBREVIATIONS

ASyS	Anti-synthetase syndrome
ACR	American College of Rheumatology
AMA-M2	Anti-mitochondrial antibody type M2
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ACC	American College of Cardiology
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CK	Creatin kinase
CADM	Clinically amyopathic dermatomyositis
CMR	Cardiac magnetic resonance
CRP	C-reactive protein
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
EULAR	European Alliance of Associations for Rheumatology
ENMC	European Neuromuscular Centre
DM	Dermatomyositis
EMG	Electromyography
ECG	Electrocardiogram
ESC	European Society of Cardiology

^{18}F-FDG	Fluorodeoxyglucose F18
GLS	Global longitudinal strain
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HRCT	High-resolution computed tomography
HAQ-DI	Health Assessment Questionnaire-Disability Index
HF	Heart failure
HFA	Heart Failure Association
IBM	Inclusion body myositis
IIM	Idiopathic inflammatory myopathies
IMNM	Immune-mediated necrotizing myopathy
ILD	Interstitial lung disease
ICD-10	International Classification of diseases, 10th Revision
IMACS	International Myositis Assessment & Clinical Studies Group
IMCCP	International Myositis Classification Criteria Project
LVEF	left ventricular ejection fraction
LGE	Late Gadolinium enhancement
LDH	Lactate dehydrogenase
MAA	Myositis-associated autoantibodies
MDA-5	Melanoma differentiation-associated protein 5
MRI	Magnetic resonance imaging
MSA	Myositis-specific autoantibodies

MCTD	Mixed connective tissue disease
NXP2	Nuclear matrix protein 2
NTproBNP	N-terminal Pro-brain natriuretic peptide
PM	Polymyositis
PYP	Technetium-99m pyrophosphate
PH	Pulmonary hypertension
PAH	Pulmonary arterial hypertension
PBC	Primary biliary cholangitis
PCI	Percutan coronary intervention
PET	Positron Emission Tomography
RA	Rheumatoid arthritis
SAE	Small ubiquitin-like modifier activating enzyme
SLE	Systemic lupus erythematosus
SRP	Signal recognition particle
sST2	Soluble suppression of tumorigenicity 2
STEMI	ST-elevation myocardial infarction
TIF 1-γ	Transcriptional intermediary factor 1-γ
TTE	Transthoracic Echocardiography

1 INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of rare autoimmune systemic rheumatic diseases which are broadly heterogeneous (1, 2). The heterogeneity of IIM arises from multiple interacting factors, both biological and clinical, including variability in immunohistopathological background (3-6), clinical manifestation (1, 7, 8), autoantibody profiles (7, 9-11), genetic predisposition (12-16), environmental exposures (17-21) and treatment responses. IIM is characterized by inflammation of skeletal muscles (leading to muscle weakness and elevated serum levels of muscle enzymes), presence of myositis-specific autoantibodies and inflammatory cell infiltrates on muscle biopsy (22). The main subgroups of IIM include adult polymyositis (PM), adult dermatomyositis (DM), juvenile dermatomyositis (JDM), immune-mediated necrotizing myopathy (IMNM), anti-synthetase syndrome (ASyS), overlap myositis and inclusion body myositis (IBM) (1, 23, 24). Extramuscular organs such as the lungs, skin, joints, and heart can also be involved in IIM (25, 26). The type of extramuscular organ involvement seems to be strongly linked to the IIM subgroup. For example, there is a well-established high risk of lung involvement in ASyS (1) with or without muscle inflammation (myositis) together with other manifestations such as Raynaud phenomenon, mechanic's hands, fever, and symmetrical small-joint arthritis (23). In DM, the most common manifestations are characteristic cutaneous rashes (Gottron's papules and heliotrope erythema) and an increased risk of malignancy (27-29) while IMNM is characterized by moderate-severe skeletal muscle involvement with markedly elevated creatine kinase (5, 30, 31). Regarding overlap myositis, any type of IIM subgroup could be associated with another autoimmune rheumatic disease (24) such as systemic sclerosis, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

In other words, different subgroups exhibit distinct patterns of extramuscular organ involvement. However, what is known regarding cardiac involvement and cardiovascular disease in IIM?

About nine years ago, a colleague asked me to give a lecture on the extramuscular manifestations in IIM and recommendations about their investigations and management. I then realized that cardiac and cardiovascular involvement in patients with IIM was among the least studied extramuscular manifestations of IIM. There was a lack of clear definition regarding cardiac involvement, its frequency, which subtypes are affected, how it should be evaluated, and what the most appropriate recommended treatment options are. At that time, most of the research on this topic consisted of retrospective studies without longitudinal follow-up. This triggered my interest in conducting research on cardiac involvement and cardiovascular disease in patients with IIM.

In this thesis, I am trying to broaden clinical awareness of cardiac involvement in IIM. I will start with a brief review of the current knowledge on the epidemiology of IIM, their classification, clinical manifestations, and myositis-related autoantibodies. Then, I will give an overview of the available evidence and current understanding of cardiac involvement in patients with IIM.

1.1 EPIDEMIOLOGY

Epidemiological studies aimed at estimating the incidence and prevalence of IIM are challenged by several factors, including heterogeneity in diagnostic criteria used for disease identification, as well as variation in environmental exposures and genetic backgrounds across different geographical regions

worldwide. For example, anti- MDA5 positive DM which is frequently associated with rapidly progressive interstitial lung disease is more commonly reported in East Asian populations, whereas IMNM and overlap myositis appear increasingly recognized worldwide due to improved serological testing (27, 31). Another example, anti-Mi-2 positive DM has an observed increased prevalence in the region closer to the Equator whereas anti- TIF1-γ and anti-NXP2 antibodies are more often described in European and American cohorts (27, 32, 33).

The overall incidence of IIM has been estimated at approximately 0.2–2 cases per 100,000 person-years and the prevalence generally ranging between 2 and 25 cases per 100,000 individuals (34). In Sweden, a nationwide population-based study estimated in adult individuals an incidence of 11 per million person/ year and a prevalence of 14 per 100,000 population (35). In England, a retrospective study observed a rise in IIM diagnoses from 3.2 to 4.3 per 100 000 person/ year (36). Furthermore, IIM incidence tends to increase with age, and peak onset occurs in the age group of 50–79 years (35).

Majority of IIM subtypes (DM, PM, ASyS and IMNM) are more common in women, while IBM is an exception with 65-70% being men (34, 35, 37-39).

1.2 CLASSIFICATION

In 1975, Bohan and Peter suggested useful criteria for classification and diagnosis of IIM that included most important variables such as type of muscle weakness, elevation of the serum levels of skeletal muscle enzymes, distinct electromyographical and skin changes, and muscle biopsy findings (40, 41). However, the Bohan and Peter criteria are limited by several factors, including the absence of myositis-specific autoantibodies and broad, relatively

nonspecific muscle biopsy findings, focusing on general features of inflammatory myopathy (Table 1).

Table 1. Modified Bohan and Peter criteria for dermatomyositis (DM) and polymyositis (PM).

First, exclude all other forms of myopathies
1. Symmetrical, progressive muscle weakness. 2. Muscle biopsy evidence of myositis (phagocytosis, degeneration and regeneration of muscle fibers, mononuclear cells in endomysial, perimysial, perivascular, or interstitial muscle tissues). 3. Elevation of muscle-associated enzyme levels. 4. Myopathic changes on electromyography. 5. Typical dermatomyositis rashes.

Definite PM: 1-4; probable PM: 3 of 1-4; possible PM: 2 of 1-4. Definite DM: 5+ 3 of 1-4; probable DM: 5+ 2 of 1-4; possible DM: 5+ 1 of 1-4.

Approximately two decades after the introduction of the Bohan and Peter criteria, several alternative classification and diagnostic criteria were developed that aimed to incorporate myositis-specific autoantibodies and enhance the diagnostic accuracy of the existing parameters (6, 42-44). The Tanimoto criteria (1995) introduced the anti-Jo-1 antibody and systemic inflammatory markers to the formal classification of IIM (42) whereas Targoff criteria (1997) expanded further the myositis-specific autoantibodies profile and validated muscle MRI as a non-invasive tool to identify active oedema/inflammation (43).

In 2017, the experts in the International Myositis Classification Criteria Project (IMCCP) developed and published new "2017 EULAR/ACR (European Alliance of Associations for Rheumatology/American College of

Rheumatology) classification criteria for adult and juvenile IIM and their major subgroups" (45). This new classification included more detailed information about the pattern of muscle weakness and the possibility of more specific histopathological patterns in muscle biopsy aiding in distinguishing between different IIM subgroups (46). It assigned weighted mathematical scores to 16 variables across six clinical and laboratory categories and included two separate scoring models: one if the muscle biopsy data is available and another when biopsy is not performed. Furthermore, the new EULAR/ACR criteria included the presence of anti-Jo-1 positivity and dysphagia (Table 2).

Anti-Jo-1 belongs to the group of anti-synthetase antibodies and is the most frequently occurring myositis-specific autoantibodies. However, patients with anti-Jo-1–positive ASyS who lack muscle involvement often do not fulfill the 2017 EULAR/ACR IIM classification criteria. Instead, more sensitive Connor`s criteria are recommended for screening of ASyS (23). To fulfill the Connor`s criteria, a patient must have the presence of any anti-synthetase autoantibody (mandatory serological criterion) in combination with at least one of the following clinical features (clinical criteria): interstitial lung disease, inflammatory myopathy, non-erosive arthritis, Raynaud's phenomenon, unexplained persistent fever, or mechanic's hands.

Another limitation of 2017 EULAR/ACR IIM classification criteria is poor performance for IMNM subclassification with 35-64% cases misclassified as non-myositis (47). The major concerns are that the muscle biopsy items focus on inflammatory infiltrates rather than necrosis, and IMNM-specific myositis-specific autoantibodies (anti-SRP, anti-HMGCR) are not included. Instead, European Neuromuscular Centre-based (ENMC) classification criteria are used (31). These criteria subclassify IMNM into three distinct serological categories (seronegative, anti-SRP positive and anti-HMGCR positive myopathy) whereas biopsy is mandatory in seronegative cases.

Table 2. Modified EULAR/ACR classification criteria for adult and juvenile IIM.

When no better explanation for the symptoms and signs exists, these criteria can be used
- Age of onset of the first symptoms: 1. ≥ 18 and < 40. 2. ≥ 40 years. -Muscle Weakness: 1. Symmetrical, progressive muscle weakness of upper extremities. 2. Symmetrical, progressive muscle weakness of lower extremities. 3. Neck flexors are weaker than neck extensors. 4. Proximal muscles in the legs are weaker than proximal muscles. -Skin manifestations: 1. Heliotrope rash. 2. Gottron´s papules. 3. Gottron´s signs. -Dysphagia or esophageal dysmotility -Laboratory findings: 1. Anti-Jo1 autoantibody. 2. Elevated levels of muscle-associated enzymes. -Muscle biopsy: 1. Mononuclear cells in endomysial tissues. 2. Mononuclear cells in perimysial and/or perivascular tissues. 3. Perifascucular atrophy. 4. Rimmed vacuoles. The variables are given different scores and the sum of the number of variables needed to be tested to define myositis and its subgroup. Once the total score is calculated, it is converted into a percentage probability with following cut-offs: • Definite IIM (Probability ≥ 90%): Requires a score of ≥ 7.5 without a biopsy, or ≥ 8.7 with a biopsy. • Probable IIM (Probability ≥ 55% to < 90%): Requires a score of ≥ 5.5 without a biopsy, or ≥ 6.7 with a biopsy. This is the recommended baseline score to officially classify a patient for clinical trials. • Possible IIM (Probability ≥ 50% to < 55%): Requires a score of ≥ 5.3 without a biopsy, or ≥ 6.5 with a biopsy. • Not IIM (Probability < 50%): The diagnosis is ruled out if scores fall below the possible threshold (45).

1.3 AUTOANTIBODIES AND IIM SUBGROUPS

Two main categories of autoantibodies can be identified in IIM: myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA). MSA can be detected in roughly 60–88% of individuals with IIM (48, 49). The discovery of these autoantibodies is considered a major scientific breakthrough in IIM that led to many benefits and advances in many aspects. First, MSA are specific and strongly associated to IIM, helping to identify and classify cases that do not fit within the current classification criteria, especially in cases in which extramuscular manifestations predominate over muscle manifestation. Second, MSA aid to make the different IIM subgroups more homogeneous by linking together clinical manifestations, histopathological findings on muscle biopsy, and the possible prognosis. Third, knowledge of the specific IIM subgroup and associated autoantibody profile assists clinicians in appropriately directing further evaluation of extramuscular organ involvement and, ultimately, in selecting the most suitable therapeutic strategy. Subsequently, the prognosis and survival of the patients with IIM will be improved.

MAA are antibodies that may be detected in IIM but also occur in other rheumatic diseases, such as systemic sclerosis, SLE, and mixed connective tissue disease (MCTD). Among the MAA that can currently be detected are anti-U1-RNP, anti-Ro/SSA, anti-PM/Scl, and anti-Ku (48, 50). Anti-cN1A antibodies, initially defined as MSA highly specific for IBM, are according to latest EMNC guidelines classified into MAA. Anti-cN1A testing should be considered if IBM is suspected (51).

Nowadays, with the aid of MSA and MAA, IIM in adults can be divided into six distinct subgroups; DM, PM, ASyS, IMNM, overlap myositis and IBM (1).

DM can be further subdivided into distinct entities, including classic DM with often positive anti-Mi2 (52, 53), clinically amyopathic DM (CADM), and cancer-associated DM (7). Patients with CADM often have positive anti-SAE or anti-MDA-5. In CADM, the patient usually exhibits predominantly typical skin manifestations, mild or no clinical muscle symptoms, and often normal levels of muscle enzymes (54-56). Anti-MDA-5 associated DM is a condition that can be associated with high incidence of life threating, rapidly progressive interstitial lung disease (54, 57). Patients with cancer-associated DM are typically older than 40 years and often exhibit positive anti-TIF1-γ or anti-NXP2 (58-60). These patients are often present with severe cutaneous and muscle inflammation (61, 62).

PM is now considered the smallest subgroup, mainly due to the recognition of newer myositis subgroups such as ASyS and IMNM (63).

ASyS is an IIM subgroup with autoantibodies directed against aminoacyl transfer RNA synthetase enzymes that are involved in protein synthesis. This distinct subgroup is characterized by myositis and/or interstitial lung disease. Other clinical features that may also be present in the majority of patients with ASyS include small-joint arthritis, Raynaud´s phenomenon, mechanic's hands, and fever. Anti-Jo1 is the most common ASyS autoantibody with a frequency up to 25% of IIM cases (8). The other ASyS autoantibodies occur to a much lesser extent (Table 3) (10).

IMNM is manifested by moderate-severe skeletal muscle involvement with very high muscle enzyme levels, severe dysphagia and specific histopathological features on muscle biopsy characterized by extensive muscle

fiber necrosis and regeneration, with minimal or absent lymphocytic infiltration (31, 64-66). IMNM can be subdivided into three distinct categories according to autoantibody status: anti–SRP–associated IMNM, anti–HMGCR–associated IMNM, and seronegative IMNM. HMGCR-associated IMNM represents the largest IMNM subgroup and accounts for approximately 6–20% of IIM cases, with the majority of cases being linked to prior statin exposure (67).

Overlap myositis is a form of IIM characterized by the coexistence of features of other connective tissue diseases such as systemic sclerosis, SLE, RA and MCTD. MAA and/or MSA are often present (24).

IBM is a subgroup of IIM that differs in several aspects from the other IIM subgroups, including being asymmetric, affecting distal muscle groups, not responding to immunosuppressive treatment, and having a characteristic histopathological muscle biopsy with rimmed vacuoles and with positive cN1A antibody in up to 76% (39, 68, 69).

Table 3. Prevalence and clinical association of MSA and MAA in IIM.

Antigen	Antibody full name	Reported prevalence range	Most typical symptoms	Associated organ involvement	IIM subtype
MSA					
Mi-2α/ β	Anti-Mi-2 alpha/ beta	5-10%	Classic DM rash, myositis	Skin, skeletal muscle	DM, juvenile DM
TIF1γ	Anti-TIF1-gamma	7%	Often marked cutaneous disease, myositis.	Skin, malignancy association, skeletal muscle	DM cancer-associated DM in adults
MDA5	Anti-MDA5	1-30%	Amyopathic or mild myositis, skin ulcers, rapidly progressive ILD, dysphagia.	Lung, skin, sometimes joints	DM, clinically amyopathic DM
NXP2	Anti-NXP2	3-25%	More severe myositis, dysphagia, classic DM rash, calcinosis.	Skeletal muscle, dysphagia, skin, sometimes malignancy in adults	DM, juvenile DM, cancer-associated DM in adult
SAE1	Anti-SAE1	3%	Prominent skin disease, mild or no myositis, dysphagia	Skin, skeletal muscle, sometimes esophagus/lung	DM, clinically amyopathic DM
Jo-1	Anti-Jo-1 / histidyl-tRNA synthetase	20-25%	Myositis, arthritis, Raynaud, mechanic's hands, fever	Lung, skeletal muscle, joints, skin	ASyS, overlap myositis
PL-7	Anti-PL-7 / threonyl-tRNA synthetase	5%	Myositis, ILD, arthritis, Raynaud phenomenon, mechanic's hands	Lung, skeletal muscle, joints, skin	ASyS
PL-12	Anti-PL-12 / alanyl-tRNA synthetase	5%	Often lung-dominant disease, sometimes minimal myositis	Lung, skeletal muscle, joints	ASyS
EJ	Anti-EJ / glycyl-tRNA synthetase	<5%	Myositis, arthritis, Raynaud, ILD	Lung, skeletal muscle, joints	ASyS
OJ	Anti-OJ / isoleucyl-tRNA synthetase	<5%	Myositis with lung disease and arthritis	Lung, skeletal muscle, joints	ASyS
Zo	Anti-Zo	<1%	Antisynthetase-spectrum phenotype	Lung, skeletal muscle, joints	ASyS
Ha	Anti-Ha	<1%	Antisynthetase-spectrum phenotype	Skeletal muscle; phenotype depends on broader overlap pattern	ASyS, overlap myositis
Ks	Anti-Ks / asparaginyl-tRNA synthetase	<1%	Antisynthetase-like features, often ILD-dominant	Lung, muscle, joints	ASyS
SRP	Anti-SRP	2%	Acute or severe myositis, very high CK	Skeletal muscle, sometimes cardiac or	IMNM

				respiratory involvement	
HMGCR	Anti-HMGCR	6-20%	Myositis,dysphagia, often statin exposure	Skeletal muscle	IMNM
MAA					
cN-1A	Anti-cN-1A	52-76% of IBM	Slowly progressive, asymmetric weakness of finger flexor and quadriceps involvement, dysphagia.	Skeletal muscle	IBM
Ro-52	Anti-Ro52 / SSA-52 kDa	25%	Often coexists with MSA and more severe lung disease	Lung, Skeletal muscle	Overlap myositis, ASyS
Ku	Anti-Ku	<1%	Overlap features, myositis, raynaud, atrhritis	skeletal muscle, lung, joints, systemic sclerosis-overlap	Overlap myositis
PM-Scl/100	Anti-PM/Scl100	<1%	Proximal weakness, raynaud, ILD, arthritis, dysphgia.	Skeletal muscle, skin, lung, esophagus	Overlap myositis
PM-Scl/75	Anti-PM/Scl75	<1%	Proximal weakness, raynaud, ILD, arthritis, dysphagia	Muscle, skin, lung, esophagus	Overlap myositis
U1RNP	Anti-U1RNP	10%	Proximal weakness, dysphagia, raynaud, ILD, arthritis, pulmonary hypertension	Muscle, lung, esophagus	Overlap myositis/ MCTD

ASyS: Anti-synthetase syndrome; cN-1A: cytosolic 5'-nucleotidase 1A; DM: Dermatomyositis; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; ILD: Interstitial lung disease; IMNM: Immune-mediated necrotizing myopathy; IBM: Inclusion body myositis; MSA: Myositis-specific antibody; MAA: Myositis-associated antibody; MDA-5: melanoma differentiation-associated protein 5; MCTD: Mixed connective tissue disease; NXP2: nuclear matrix protein 2; SAE1:SUMO activating enzyme 1; SRP: signal recognition particle; TIF1γ: transcription intermediary factor 1-gamma. Mchugh *et al.* (48), Ogava-Momohara *et al.* (7), Hervier *et a.l* (70), Herbert *et al.* (69).

1.4 CLINICAL MANIFESTATIONS IN IIM

Figure 1 provides an overview of the clinical manifestations associated with IIM.

1.4.1 MYOSITIS

Myositis (muscle inflammation) manifests as progressive muscle weakness and reduced endurance. Muscle tenderness and swelling may also occur. Muscle symptoms are typically symmetrical and affect the proximal muscle groups (45). Muscle enzymes such as creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) are usually elevated. Myoglobin, a sensitive biomarker of muscle damage, is often increased as well. To confirm the presence of

myositis, electromyography (EMG) and muscle biopsy are highly recommended (41, 45), especially in the absence of elevated CK and/or positive MSA. EMG and muscle biopsy are informative both in confirming the presence or absence of myopathic changes and in excluding or confirming other neuromuscular disorders. Additionally, muscle biopsy findings play a crucial role in distinguishing between the various subgroups of IIM (63).

Muscle magnetic resonance imaging (MRI) is sometimes used to identify the presence and location of muscle oedema, aiding in selecting an area for biopsy. It can also identify muscle atrophy and fat replacement that can be seen in the later stage of the disease (71, 72).

1.4.2 SKIN MANIFESTATIONS

Patients with dermatomyositis exhibit a range of cutaneous manifestations; some are characteristic for the disease, whereas others are non-specific and may also occur in other conditions (73). The cutaneous manifestations specific to dermatomyositis include Gottron's papules and heliotrope rash (41, 45). Gottron's papules are purple-red, slightly elevated plaques that occur symmetrically over extensor surfaces of hands joints, while heliotrope rash is a symmetrical purple-lilac rash involving the upper eyelids, commonly associated with periorbital swelling (74). A range of other non-specific cutaneous manifestations may also be observed in patients with IIM, and those include malar/facial erythema, V-sign, Shawl sign, ulceration, erythroderma, periungual capillary changes, mechanic´s hands, calcinosis and alopecia (75, 76).

1.4.3 LUNG INVOLVEMENT

Interstitial lung disease (ILD) represents one of the most frequent extramuscular manifestations of IIM. The most well-recognized and prevalent forms of ILD in patients with IIM are non-specific interstitial pneumonia, usual

interstitial pneumonia, organizing pneumonia or diffuse alveolar damage (77-79).

ILD is especially common in patients with ASyS and anti-MDA-5 positive DM (80). ASyS patients with positive anti-SSA-52 tend to develop more frequent and aggressive pulmonary disease (81, 82). Anti-MDA-5 positive DM is often associated with worse ILD outcomes because of its acute and rapidly progressive pattern (83, 84).

Pulmonary function tests such as spirometry, including measurement of the diffusing capacity of the lung for carbon monoxide, together with high-resolution computed tomography (HRCT) are commonly used to diagnose ILD in IIM. These investigative methods are also valuable for monitoring lung function and lung disease activity over time and assessing the response to therapy (85-87).

1.4.4 **HEART**

This topic will be discussed in detail in the following sections.

1.4.5 **JOINTS**

Joint involvement in IIM may occur in certain subgroups at rates of up to 55% (88). The articular manifestations may present as arthralgia or arthritis and often affect the small joints of the hands. The symptoms are typically symmetric and may clinically resemble RA. Joint involvement is observed particularly in certain forms of myositis, such as ASyS and overlap myositis, and may be associated with specific autoantibodies (80, 89) (Table 3). In contrast to classical RA, joint involvement in myositis is most often non-erosive (42). Arthritis or arthralgia may occasionally represent the initial manifestation of IIM, which can result in patients being misdiagnosed with RA at IIM presentation.

1.4.6 **GASTROINTESTINAL MANIFESTATIONS**

Most common gastrointestinal manifestation in IIM is esophageal involvement which results in difficulty in swallowing (dysphagia) with bad consequences such as malnutrition and aspiration pneumonia (90). It can be presented in all IIM subgroups, but severe or refractory dysphagia is mostly observed in patients with anti-MDA-5 positive DM, cancer-associated IIM and IBM (90-92). Dysphagia is one of the scoring items included in the 2017 EULAR/ACR classification criteria (45).

Other gastrointestinal manifestations such as small intestinal dysmotility, inflammatory bowel diseases, and hepatic disorders are less common in IIM (93).

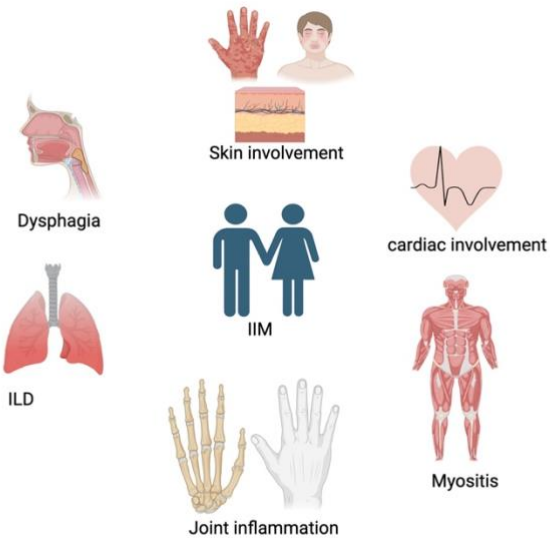

Figure 1 Clinical manifestations in IIM. ILD: interstitial lung disease.

2 MYOCARDITIS AND PERICARDITIS

2.1 MYOCARDITIS AND PERICARDITIS IN AUTOIMMUNE DISEASES

Myocarditis is a non-ischaemic inflammation of the heart muscle, and the inflammation may involve the myocardium in a focal or diffuse pattern which can be present as acute, subacute or chronic (94-96). Myocardial inflammation can also extend into the pericardium, causing myopericarditis. In general, the reported prevalence of myocarditis across the world was 10-105 per 100,000 in 2021 (97). Ren *et al.* observed an increased trend in myocarditis incidence with an age-standardized incidence rate of approximately 16 per 100,000 people (98). In Sweden, Fu *et al.* reported a myocarditis incidence ranging from 6.3 to 8.6 per 100,000 inhabitants in a population-based cohort study (95).

Clinical manifestations of myocarditis are non-specific symptoms (including dyspnoea, chest pain, palpitations and syncope), unspecific changes at electrocardiogram (ECG) and /or arrhythmia. If these manifestations do not resolve spontaneously or are not treated, this can result in heart failure, cardiogenic shock and/or sudden cardiac death (94, 96, 99). Owing to the subclinical nature of myocarditis, some cases were identified incidentally through post-mortem heart biopsy (100, 101).

Myocarditis is one of the major mechanisms of myocardial damage in many autoimmune rheumatic diseases including SLE, systemic sclerosis, RA, vasculitis, sarcoidosis, and IIM (94, 102, 103). Both clinical and subclinical forms of myocarditis have been reported in autoimmune rheumatic diseases (102). However, the rate of subclinical myocarditis seems to be more common than clinically manifested myocarditis (100, 104-108).

In SLE, clinically apparent myocarditis has been reported by Cheng *et al.* in up to 3-9% of patients while in another study, based on autopsy finding, the reported rate of myocarditis was 40-70% (109, 110). In systemic sclerosis, the incidence of myocarditis ranges from 10 to 30 % (107, 111, 112). Regarding RA, post-mortem studies have identified myocarditis in approximately 19% of RA patients, most of whom were clinically asymptomatic (113). Furthermore, Kobayashi *et al.* revealed a higher rate of myocardial delayed enhancement in around 38 % in asymptomatic RA patients using cardiac magnetic resonance (114). In sarcoidosis patients, myocarditis has been reported in approximately 5-30% (99, 115).

Although myocarditis associated with autoimmune diseases is often responsive to DMARD and corticosteroid treatment, its frequently subclinical presentation may lead to underdiagnosis and missed therapeutic opportunities, thereby increasing the risk of mortality (99, 102).

Pericarditis is an inflammation of the pericardium and may occur in several autoimmune rheumatic diseases. Pericarditis can present in several forms (116, 117):

1. Acute pericarditis, which is the most common form characterized by chest pain relieved by sitting forward.
2. Chronic pericarditis which may sometimes result in fibrosis and scarring.
3. Constrictive pericarditis, a consequence of chronic or recurrent acute pericarditis, in which the pericardium becomes thickened, fibrotic and often calcified, leading to restriction of normal diastolic cardiac filling.
4. Cardiac tamponade, which is a large pericardial effusion with serious life-threatening hemodynamic consequences. It impairs cardiac filling and cardiac output resulting in hypotension and shock.

Pericarditis in RA and SLE is the most frequently observed cardiac manifestation (118, 119). In SLE, symptomatic pericarditis is reported to occur up to about 25% throughout the course of the disease (120). Another review by Moder *et al.* estimated that pericarditis, both symptomatic and asymptomatic, may occur in 12-48% in patients with SLE (121).

Even in patients with RA, clinically symptomatic pericarditis is estimated to occur in fewer than 10% of cases and is less prevalent than asymptomatic pericarditis. Echocardiographic and autopsy studies suggest that the prevalence of pericarditis may reach up to 30-50% in patients with RA (122).

2.2 MYOCARDITIS IN IIM

In 1899, Oppenheim was the first to describe a case of a patient with polymyositis presenting cardiac muscle involvement (123) and many years after that, the cardiac manifestation was regarded as a rare extramuscular manifestation of IIM. In the 1970s, it became increasingly evident that cardiac involvement in IIM might not be an uncommon manifestation. In 1977, Bohan *et al.* reported in a retrospective study ST-T abnormalities on electrocardiography in 24% and 18% of patients with PM and DM, respectively (124). The presence of ST-T changes on electrocardiography generally reflects underlying cardiac pathology and heart muscle injury and therefore some of these abnormalities may have been attributable to myocarditis.

Clinically obvious cardiac involvement in IIM is uncommon and occurs in less than 10% of patients. Therefore, myocarditis in IIM is often subclinical, without apparent cardiac symptoms and remains challenging to diagnose and manage in a timely manner (125-127). If myocarditis is symptomatic, it most

commonly presents with chest pain, palpitations, dyspnea, syncope, cardiogenic shock, or symptoms consistent with heart failure (128, 129).

Due to the predominantly subclinical pattern of myocarditis, its true prevalence has been difficult to determine. To date, the reported prevalence of myocarditis in IIM is ranging from 3.4% to 62%. One reason for the wide variability is that different studies use diverse diagnostic methods to assess cardiac involvement and myocarditis in IIM. Another contributing factor is various study designs, as some studies are retrospective and registry-based, whereas others are cross-sectional or prospective longitudinal.

In an autopsy-based study by Haupt *et al*. 25% of IIM patients had evidence of active myocarditis (130). In another autopsy-based study by Denbow and collogues, the histopathological examinations revealed myocarditis in 6 of 20 autopsied patients with IIM, corresponding to a prevalence of 30% (131).

Based on cardiac magnetic resonance (CMR) findings in a study from 2015 by Rosenbohm *et al*. 62.3% of included IIM patients exhibited signs of myocardial inflammation (132). Of note, patients with IMNM were excluded, and cardiac troponin levels were not analyzed in this study. A retrospective study by Mavrogeni *et al.* showed a silent myocardial involvement in 56.3% of IIM patients as diagnosed by positive late gadolinium-enhanced on CMR (133). Two years later, the same author demonstrated in a prospective study that 55% of patients with acute inflammatory myopathies had concomitant ongoing myocarditis (134) as evidenced by CMR. A register-based study reported prevalence of myocarditis of 3.4% among patients with ASyS (135) while in another study of 25 patients with ASyS, 32% showed pathological changes on CMR suggestive of ongoing or previous myocarditis (126). Lim *et al.* described a cohort of 34 patients with IIM, of whom 24% had CMR findings indicative of definite or probable myocarditis (136). Markousis-Mavrogenis *et*

al. used CMR to evaluate myocarditis according to the updated Lake Louise criteria in 28 patients with IIM who were referred to a cardiology unit due to cardiac symptoms. Twenty age- and sex-matched healthy controls were also included in the study. Twenty-seven IIM patients (96%) demonstrated evidence of acute myocardial inflammation (137). Khoo *et al*. demonstrated that 9 of 19 (47%) patients with IIM without cardiac symptoms exhibited focal or diffuse myocardial fibrosis according to CMR investigations (138). Buchpiguel and colleagues used Technetium-99m pyrophosphate (PYP) scintigraphy to detect cardiac muscle inflammation and observed increased cardiac PYP uptake in 57% of IIM patients (139). Finally, a recently published study of 26 newly diagnosed patients with IIM reported that 27% had myocarditis as detected by CMR imaging (140).

In **paper I**, we enrolled 109 patients with established IIM, with a median disease duration of 32 months. Out of 109, 14 patients (13%) had previously experienced myocarditis during the course of their disease. IIM patients were considered to have myocarditis if they exhibited pathological elevations in cTnI levels, and/or revealed signs of myocarditis by CMR (as evidence of cardiac involvement related to IIM), and one of the following:

1) Cardiac symptoms, such as chest pain, palpitations, or dyspnoea (note: dyspnoea attributable to concomitant interstitial lung disease or other pulmonary conditions was not considered indicative of cardiac involvement).

2) Abnormalities in both electrocardiography (ECG) and transthoracic echocardiography (TTE) consistent with myocarditis.

In **paper II**, we described 34 newly diagnosed patients with IIM and 9 healthy controls who underwent CMR, electrocardiographic, and echocardiographic evaluation. CMR findings indicated that 35% of the patients exhibited features

consistent with ongoing or prior myocarditis. None of the healthy controls exhibited myocarditis changes on CMR.

2.3 PERICARDITIS IN IIM

Pericarditis is not uncommon presentation in patients with IIM, and it may occur either as an isolated manifestation or in conjunction with myocarditis. In adults with IIM, pericarditis is mostly subclinical with a reported prevalence range from 4-25% (141). However, Liu and colleagues reported that pericardial effusion was present in > 30% of patients with IIM, of whom 19% concurrently exhibited myocarditis (142). Pericarditis leading to cardiac tamponade and hemodynamic compromise can occur in patients with IIM, although it is rare (143). Chung *et al.* observed that 5 of 12 IIM patients revealed pericardial effusion and none exhibited negative hemodynamic consequences (128). In a French, registry-based retrospective study, TTE revealed pericarditis in 6 of the 12 patients with ASyS-associated myocarditis (50%)**,** whereas in one of these cases the pericarditis was relapsing and caused hemodynamic compression (135). A European multicentre study suggested that pericarditis can be a possible manifestation in anti-PL-7 positive ASyS, as 50% of patients exhibited pericarditis (144).

In **paper II**, using CMR data, we described that pericarditis was observed in 6 patients with newly diagnosed IIM (17.6%), of whom 2 cases were associated with simultaneously myocarditis. None of the patients with pericarditis exhibited significant hemodynamic consequences (127). Using TTE, only one of those 6 IIM patients demonstrated evidence of pericarditis, suggesting the majority of cases were likely subclinical and detectable only by CMR. The autoantibody profile among these IIM patients was following: 2 patients with

positive anti-HMGCR, 1 patient with positive anti-TIF1-γ, 1 patient with positive anti-Mi-2β, 1 patient with positive anti-Jo-1 together with anti-SSA-52 whereas 1 patient was seronegative.

3 CARDIOVASCULAR DISEASES AND RISK FACTORS IN IIM

3.1 TRADITIONAL CARDIOVASCULAR RISK FACTORS IN IIM

Patients with IIM exhibit an increased prevalence of traditional cardiovascular risk factors, including hypertension, dyslipidaemia, diabetes mellitus, obesity, smoking, and physical inactivity. These findings are in line with observations from other autoimmune rheumatic diseases such as RA and SLE (145-149). Prieto *et al*. conducted a retrospective, matched, population-based cohort study, in which they included 603 patients with IIM, 4047 patients with RA and 4061 healthy controls (150). The study reported a significantly greater prevalence of traditional cardiovascular risk factors, including current smoking, hypertension, diabetes mellitus, dyslipidaemia, and obesity, among patients with IIM and RA, compared to healthy controls (150).

A systematic review and meta-analysis of nine studies, in which the number of patients with IIM ranged from 28 to 4958 and the mean age of IIM cohorts varied between 42.9 and 62.2 years, demonstrated that hypertension, diabetes mellitus and dyslipidaemia were more prevalent among patients with IIM compared with control individuals (151).

A retrospective study from south Australian observed a higher-than- expected prevalence of hypertension and diabetes mellitus among patients with IIM, with reported prevalences of 62% and 29% for hypertension and diabetes mellitus, respectively (152).

A cross-sectional, case-control study by Oreska *et al*. included 90 patients with IIM and 180 healthy controls. The authors reported a significantly higher

prevalence of hypertension, dyslipidaemia and diabetes mellitus among IIM patients compared to healthy controls (153).

Similarly, a cross-sectional, observational study by Diederichsen *et al*. reported a significantly higher frequency of hypertension, diabetes mellitus and overweight, as well as significantly higher levels of triglycerides in IIM patients in comparison to healthy controls (154).

Furthermore, components of metabolic syndrome have been reported with higher prevalence in patients with IIM than in healthy controls. Metabolic syndrome is a condition defined by the clustering of abdominal obesity, dyslipidaemia, hypertension, and impaired glucose metabolism, and is associated with a substantially increased risk of cardiovascular diseases (155, 156). A cross-sectional, case-control study revealed a higher frequency of metabolic syndrome in patients with ASyS compared to healthy controls, with prevalences of 43% and 13%, respectively (157). Two additional studies reported similar findings in patients with PM and DM (158, 159). De Souza *et al.* demonstrated an association between corticosteroid treatment and metabolic syndrome. In that study, PM patients with metabolic syndrome had received higher cumulative prednisolone doses (159). Furthermore, IIM patients with long time exposure to corticosteroid treatment might exhibit a higher risk for atherosclerosis development (153).

With regard to physical activity, several cohort studies have demonstrated inverse association between physical activity and the incidence of cardiovascular diseases, with higher levels of activity associated with lower risk of total cardiovascular diseases (160, 161). Patients with IIM frequently suffer from muscle weakness and fatigue, which in turn leads to decreased physical activity (162, 163). Limaye *et al.* observed that muscle weakness was one of the important risk factors for mortality among IIM patients (164).

The results presented in **paper I** are consistent with the above-mentioned reports. Diabetes mellitus and dyslipidaemia were more frequent among our patients with IIM compared with healthy controls, and the patients with IIM had a significantly higher body mass index (BMI) in comparison to healthy controls (165). Furthermore, the prevalence of obesity (BMI > 30 kg/m^2) was higher among patients with IIM than among heathy controls. Although the number of obese individuals was greater in the IIM group, the difference did not reach statistical significance (P = 0.06).

In **paper IV**, we reported that the prevalence of cardiovascular risk factors in the prospective newly diagnosed IIM patient cohort did not increase significantly at 24 months of follow-up compared with baseline.

3.2 CARDIOVASCULAR DISEASES IN IIM

Cardiovascular diseases are not uncommon and represent major determinants of morbidity and mortality in IIM (166-169). More than one-third of patients with IIM have a moderate to high risk of experiencing cardiovascular events within ten years after diagnosis (170).

The increased prevalence of cardiovascular diseases in patients with IIM has been suggested to be attributable to several factors, including direct cardiac involvement such as myocarditis; systemic inflammation, which may accelerate atherosclerotic processes; and/ or a higher prevalence of traditional cardiovascular risk factors (141). The cardiovascular diseases observed in patients with IIM include ischaemic heart disease, heart failure, arrhythmias and pulmonary hypertension.

3.2.1 ISCHAEMIC HEART DISEASES

Ischaemic heart diseases, also known as coronary artery diseases, are a group of clinical conditions characterized by myocardial ischaemia, mostly caused by atherosclerotic narrowing or obstruction of the coronary arteries (171, 172). Several studies have demonstrated that patients with IIM have higher prevalence of atherosclerosis than healthy controls (153, 173). Diedrichsen *et al.* reported that severe coronary artery calcification occurred significantly more frequently in patients with IIM; however, it was not associated with IIM per se, but rather with age and smoking in these patients (154). Fisher *et al.* studied retrospectively the incidence of ischaemic heart disease and overall atherosclerotic cardiovascular disease (ASCVD), including cerebrovascular events, in 1899 PM/DM patients and 7676 matched controls (174). They found that patients with PM/DM exhibited a higher incidence rate of ischaemic heart disease with an adjusted hazard ratio of 1.61 (95% CI:1.15-2.25) as well as a higher incidence rate of ASCVD with an adjusted hazard ratio of 1.75 (95% CI: 1.35-2.27). Additionally, patients with PM/DM >41 years of age had a significantly higher rate of major cardiovascular events compared to the controls, with hazard ratio 1.97 (95% CI: 1.49-2.59) (174). A review by Noboa *et al.* demonstrated that patients with IIM have an approximately two-fold increased risk of ASCVD and other cardiovascular events (175).

Regarding acute coronary disease, Leclair and colleagues in Sweden found that the incidence of acute coronary syndrome was significantly higher in patients with IIM than in the general population, particularly during the first year after diagnosis and among older individuals. The overall incidence rate in patients with IIM was 15.6 per 1,000 person-years (176). A meta-analysis of 7 studies on coronary heart disease demonstrated that patients with IIM exhibited a statistically significantly increased risk for coronary heart disease with a pooled risk ratio of 2.19 (95% CI: 1.40-3.42). When subgroups of coronary

heart disease were examined, the pooled risk ratios for myocardial infarction and acute coronary syndrome were 2.27 and 2.30, respectively (151). Another meta-analysis showed similar findings, with a pooled risk ratio for coronary artery disease in patients with IIM being 2.24 (95% CI: 1.02-4.92) (177). Rai *et al.* demonstrated an increased risk for myocardial infarction in patients with PM and DM, with incidence rates of 22.5 and 12.5 per 1000 person-years, respectively (178).

3.2.2 **HEART FAILURE**

Heart failure (HF) is a clinical syndrome that develops as a result of a structural and/or functional impairment of the heart, leading to elevated intracardiac pressures and/or inadequate cardiac output. The most common symptoms that patients with heart failure experience are dyspnoea, ankle swelling and fatigue (179). HF is a major global health problem with an estimated worldwide prevalence of approximately 1-4% among adults and a higher rate in older populations (180, 181). The causes of HF are many and include ischaemic heart disease, hypertension, interstitial lung disease, pulmonary hypertension, rheumatic heart disease, myocarditis, arrhythmias, cardiomyopathies, chronic kidney disease, and chronic liver disease (180, 181).

In a review article by Gupta *et al*. the prevalence of congestive HF in IIM was reported to be approximately 5.6-11.7% (166). In a retrospective cohort study, assessing the risk of HF in 2025 patients with PM and DM, the cumulative incidence of HF increased during the follow-up period, and within 10 years follow-up, the cumulative incidence reached 7.4%. Furthermore, when compared to the general population, patients with PM and DM exhibited higher risk for HF with a hazard ratio of 2.06 (95% CI, 1.36-3.12) (182). HF can occur relatively early in the disease course. Kasser *et al.* observed that patients with

abnormalities on cardiac investigations (ECG, TTE, CMR) developed HF significantly more rapidly than those without such abnormalities, with median time 9 versus 84 months, respectively (183).

HF may result from systolic dysfunction, diastolic dysfunction, or both. Based on systolic function of the heart as measured by the left ventricular ejection fraction (LVEF), HF can be divided into 3 distinct phenotypes: HF with reduced LVEF ≤ 40%, HF with mildly reduced LVEF 41% and 49%, and HF with preserved LVEF ≥ 50% (179, 181). On the other hand, left ventricular diastolic dysfunction results from mechanical abnormalities, including decreased ventricular distensibility, delayed relaxation, and elevated diastolic filling pressure.

Peter *et al*. observed significantly lower left ventricular systolic and diastolic function in IIM patients with chronic disease course compared to IIM patients with stable disease at the two-year follow-up after diagnosis (184). Chung *et al.* reported that 71% of IIM patients with myocarditis had LVEF < 50% (128).

A review of the literature suggests that left ventricular diastolic dysfunction appears to be a recurrent and frequently reported finding in patients with IIM. Diederichsen and colleagues found that 63% of patients with PM and DM had left ventricular diastolic dysfunction and that was significantly more frequent than in healthy controls (27%, P<0.0001). Additionally, left ventricular diastolic dysfunction was associated with disease duration, suggesting that disease progression over time may affect the diastolic function of the heart in these patients (185). Similar results were previously observed by Wang and colleagues, who reported a high occurrence of left ventricular diastolic dysfunction and its association with disease duration (186).

Systolic function of the heart can also be assessed using global longitudinal strain (GLS), which is sometimes superior to ejection fraction, as it can detect subtle myocardial dysfunction earlier and more sensitively (187, 188). Left ventricular GLS normally ranges from approximately −18% to −22%, with values between −16% and −18% considered borderline and less than −16% considered abnormal (189, 190). Both TTE and CMR can be used to measure GLS. Guerra *et al*. conducted a case-control study including 28 patients with IIM and 28 matched controls to detect subclinical ventricular dysfunction in IIM by echocardiography (191). They found no significant difference between the groups regarding LVEF, while GLS values were significantly impaired in patients with IIM compared with matched controls, suggesting that subclinical systolic dysfunction is common in patients with IIM (191). Wang *et al.* used CMR to evaluate the role of strain analysis to detect cardiac involvement in IIM patients with preserved ejection fraction and found that GLS values were significantly reduced in patients with IIM (192).

In **paper I**, we found that 8 patients with established IIM exhibited GLS ≤ -18%, and one of these exhibited LVEF < 50%. In **paper II**, we found that among 34 newly diagnosed IIM patients, 6 exhibited GLS ≤ -18%. Of these, 3 also had LVEF ≤ 40% as well as CMR findings consistent with myocarditis. Furthermore, 6 IIM patients exhibited diastolic dysfunction, 5 of whom had normal GLS and LVEF, whereas 3 of these had CMR findings consistent with myocarditis or pericarditis. These results indicate that a total of 11 patients (32%) in our cohort exhibited TTE findings suggestive of HF and 6 of these cases the HF might have been related to myocarditis or pericarditis. In **paper IV,** which represents the 24-month follow-up data of 34 patients with IIM, we found that 2 patients exhibited GLS ≤ -18%, diastolic dysfunction and LVEF ≤ 50%; 2 patients had both GLS ≤ -18% and diastolic dysfunction; and 3 patients had either GLS ≤ -18% or diastolic dysfunction. These results indicate

that 10 patients (29%) in this cohort exhibited findings suggestive of suspected or overt HF.

3.2.3 **ARRHYTHMIA**

Arrhythmias are disorders of heart rhythm caused by abnormalities in the cardiac electrical system. In rheumatic autoimmune diseases, the myocardium, conduction system, coronary vessels, and cardiac valves may be affected due to inflammation, fibrosis, ischaemia, or structural remodeling, resulting in different types of arrhythmias (193-195). In IIM, arrhythmias are common, and the most observed types are supraventricular and ventricular arrhythmias, bundle branch blocks, and atrioventricular blocks (196, 197). Naaraayan *et al.* reported a significantly higher prevalence of all types of arrhythmias in patients with PM and DM compared to matched population controls ($P<0.001$), with a higher prevalence among patients aged < 70 years. Supraventricular arrhythmias, such as atrial fibrillation/flutter and supraventricular tachycardia, were the most common types of arrhythmias (198). Using Holter-ECG, Diederichsen *et al*. observed a higher frequency of supraventricular tachyarrhythmias in patients with PM and DM compared with healthy controls (185).

Persistent or recurrent arrhythmias are associated with poor prognosis, as they may be complicated by heart failure, stroke, and in severe cases even cardiac arrest and death (199-201). Huang and colleagues investigated retrospectively survival among IIM patients with myocardial involvement. The three-year survival among IIM patients with ventricular arrhythmias was significantly lower than among those IIM patients without ventricular arrhythmias, suggesting that the presence of ventricular arrhythmias is associated with adverse outcomes in IIM patients with cardiac involvement (202).

As reported in **paper I**, we detected arrhythmias in 18% of patients with established IIM disease. Supraventricular arrhythmias were the most common type.

As reported in **paper II**, we detected arrhythmias in 29% of patients with newly diagnosed IIM and the most common types were supraventricular as well as ventricular arrhythmias.

3.2.4 PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a pathophysiological condition characterized by increased pulmonary arterial pressure that may be associated with various cardiovascular and respiratory diseases, such as left ventricular dysfunction, valvular disease, ILD and chronic thromboembolic pulmonary disease (203, 204). PH is a well-recognized and clinically significant complication of several rheumatic diseases (205, 206) due to the high prevalence of ILD and left ventricular dysfunction. Furthermore, pulmonary arterial hypertension (PAH) is represents an important subgroup of PH in patients with rheumatic diseases, such as systemic sclerosis, MCTD, RA and SLE (207). PAH is a potentially life-threatening complication in these patients that may exhibit rapid progression, contributing to right ventricular dysfunction (208, 209). Signs of PH can be detected by ECG and TTE but the gold standard method for confirming the diagnosis and hemodynamic classification of PH is right heart catheterization. PH in IIM is frequently associated with ILD, where chronic inflammation, fibrosis, and hypoxia lead to pulmonary vascular remodeling and increased pulmonary arterial pressure. Other causes of PH include pulmonary vasculopathy, left-sided heart disease, and chronic thromboembolic disease.

In a Chinese cohort of 504 patients with IIM, 5% of patients exhibited PAH, and the mortality rate was high, reaching up to 48% within six months. Several

factors, such as older age, elevated disease activity, anti-SRP antibody positivity, and steroid monotherapy, were significantly correlated with the development of PAH in IIM (210). In another Chinese multicenter study of 61 patients with PM examined by TTE, the prevalence of PH was 16.4%. Additionally, 70% of those patients had ILD and 60% had pericardial effusion, suggesting that ILD and pericardial effusion may be possible contributing factors for PH (211).

Sanges and colleagues analyzed data from French PH registry and found that among 5223 patients with PH, 34 had a documented diagnosis of IIM. Most of these 34 patients with IIM-PH had evidence of ILD or overlap syndrome (212). Hervier *et al.* observed that prevalence of PH in patients with ASyS was 23.2% and all cases exhibited concomitant ILS. Furthermore, the three-year survival rate among these patients with ASyS and PH was 58% indicating an unfavorable prognosis for ASyS complicated with PH (213). Machado *et al.* observed that elevated pulmonary artery systolic pressure was significantly more prevalent compared with healthy controls only in patients diagnosed with ASyS (214).

In **paper I**, we reported that the frequency of suspected PH, defined as pulmonary artery pressure > 35mmhg, among IIM patients with established disease was relatively high (23%) and did not correlate with ILD. Suspected PH cases in our study were mostly identified by TTE, and only 2 cases were confirmed to have PAH using right heart catheterization.

4 PREDICTIVE FACTORS

Identifying predictors of cardiac involvement in IIM is essential for risk stratification and early intervention. Previous studies have suggested that both clinical characteristics and serological markers, including MSA, may be associated with an increased risk of cardiac manifestations.

In a two-year follow-up study, Peter *et al*. monitored 28 patients with IIM without cardiac involvement at baseline (184). Compared with patients with a stable disease course, patients who experienced recurrent disease flares exhibited significantly worse systolic and diastolic cardiac function at the end of follow-up, as assessed by TTE. The authors conclude that a polyphasic disease course may be associated with an increased risk of subsequent cardiac dysfunction in patients with IIM (184). A study by Machado *et al*. followed 61 patients with established IIM for approximately 25 months. They observed that patients with impaired GLS at baseline experienced more frequent disease flares and exhibited a lower mean LVEF at the 25-month follow-up compared with baseline values (214). This indicates that GLS may serve as a predictive marker of both disease activity and cardiac deterioration in IIM. A retrospective analysis published in 2023 by Chung *et al*. found that 79% of IIM patients with myocarditis had concurrent active myositis. Additionally, 93% of these patients required hospitalization and 71% exhibited features of HF with LVEF < 50% respectively (128). Similarly, our prospective study (**paper II**) demonstrated that active myositis was significantly more frequent in IIM patients who had cardiac involvement (94%) compared with IIM patients without cardiac involvement (55%). The observed positive correlation between active myositis and myocarditis may be explained by the structural similarities between the myocardial and skeletal muscles. Furthermore, we found in our study that male patients exhibited the most severe cardiac inflammation among

patient with IIM and cardiac involvement. This may suggest that male patients with IIM are at a higher risk of developing more severe cardiac inflammation than female patients. A recent meta-analysis published in 2022 demonstrated that the relative risk of cardiovascular events in men with IIM was 43% higher than in women with IIM (95% CI: 1.17–1.74) (215).

Previous studies have proposed an association between certain antibodies and cardiac involvement such as myocarditis in patients with IIM. Few small cohort studies have reported an association between anti-SRP antibodies and cardiac involvement in IIM. As early as 1990, a study by Targoff *et al.* reported that patients with anti-SRP antibodies may exhibit cardiac abnormalities, such as ECG changes and arrhythmias, suggesting potential cardiac involvement in this subgroup (216). A retrospective, multi-centre European study conducted by Hengstman and colleagues, including 23 patients with anti-SRP positive IIM, found that more than half of the patients exhibited abnormalities on ECG and/ or cardiac ultrasound. However, these investigation modalities did not confirm any myocarditis or pericarditis (217). In this context, it is difficult to draw definitive conclusions in the absence of CMR, as CMR is considered the gold-standard imaging modality for the detection of myocarditis according to international cardiology guidelines. Bandeira *et al.* demonstrated that anti-SRP antibodies were significantly more prevalent among IIM patients with cardiac involvement compared to those without (27.3% vs 5.2%, p=0.026), independent of sex, age, ethnicity and lung involvement (218). Liu *et al.* investigated cardiac involvement in a cohort of 57 patients with IMNM and found (using ECG and/ or cardiac ultrasound) evidence of cardiac involvement in 52% of cases. Notably, 53% of the patients were positive for anti-SRP antibodies (219). However, the evidence remains inconsistent, and some reports have not demonstrated a significant correlation, suggesting a heterogeneous clinical phenotype (220, 221).

Patients with anti-MDA-5 positive DM are at high risk of severe pulmonary involvement, and cardiac involvement has also been reported in this patient group (222, 223). Zhou *et al.* enrolled 76 hospitalized patients with anti-MDA-5 positive DM. Myocardial abnormalities on TTE and/or CMR were observed in twelve (15,8%) patients (224). Wang *et al.* prospectively evaluated cardiac involvement in 37 patients with anti-MDA-5 positive IIM. These patient groups exhibited significantly lower LVEF compared to healthy controls. CMR imaging demonstrated that native T1 mapping and T2 mapping values were significantly higher in patients compared to controls and 40.5% of patients exhibited evidence of myocardial fibrosis (late gadolinium enhancement) (225).

Anti-mitochondrial antibody type M2 (AMA-M2), a subtype of AMA originally recognized as a biomarker for primary biliary cholangitis (PBC), has been increasingly associated with cardiac involvement in IIM in several studies. Shi *et al.* observed that AMA-M2 positivity constituted an independent risk factor for heart failure with preserved ejection fraction and was associated with an adverse prognosis (226). Dong *et al*. stratified patients with IIM into two categories: category I, characterized by functional and/or structural cardiac involvement and category II, in which active myositis and ILD were the predominant manifestations. A significantly higher proportion of patients in category I was positive for AMA-M2 (53%, n=21) compared with those in category II (5.6%, n=3). Notably, only 2 patients in category I were diagnosed with PBC (227). Two different studies suggest that AMA-M2 positive myositis represents a distinct clinical subtype of IIM, characterized by a higher prevalence of cardiac involvement, particularly arrhythmias and conduction abnormalities. In some cases, cardiac manifestations may be severe and refractory to immunosuppressive therapy (228, 229). In a recent large cohort study of 987 patients with IIM, 6% were positive for AMA-M2. The

prevalence of cardiac involvement was significantly higher among AMA-M2 positive patients compared with those who were AMA-M2 negative (230). Consequently, AMA-M2 may serve not only as a serological marker but also as a potential indicator of increased cardiovascular risk in patients with IIM.

Some studies have suggested an association between certain MAA, such as anti-SSA (Ro) and anti-Ku, and cardiac involvement in IIM. However, the evidence remains limited and inconsistent (140, 231).

5 PROGNOSIS

The estimated overall 5-year survival in patients with IIM in 2004 ranged from 52% to 95% (232). The major causes of death in patients with IIM during the first year after the diagnosis are malignancies, and diseases of the circulatory and respiratory systems (233). Thus, cardiovascular involvement is a major contributor to mortality in IIM (234). A long-term follow-up study by Danieli *et al.* demonstrated that survival in patients with IIM has improved with appropriate immunosuppressive treatment, although prognosis remains influenced by the presence of extramuscular involvement and disease severity (235). As early as 1986, it became evident that cardiac involvement in IIM is a major contributor to mortality and is associated with poorer outcomes (236). A longitudinal study by Dankó *et al.* demonstrated relatively favorable long-term survival in patients with IIM; however, cardiac involvement emerged as one of the strongest independent predictors of mortality and a major contributor to disease-related death, as 11 of the 15 IIM patients with cardiac involvement died (232). In a single-center retrospective study by Chung *et al.*, 14 patients with IIM and clinical myocarditis were identified and followed longitudinally. The authors demonstrated that the five-year survival rate following myocarditis was 53%. All patients who died had LVEF < 40%, suggesting that myocarditis is associated with impaired cardiac function and increased mortality (128). However, it is likely that the study included patients with more severe and clinically overt myocarditis, while subclinical forms were not captured.

Severe myocarditis may lead to fibrosis, resulting in permanent myocardial damage with heart failure and arrhythmias (142). Liu *et al*. reported a significant higher frequency of electrocardiographic and echocardiographic abnormalities in IIM patients with myocarditis compared with IIM patients

without myocarditis (142). Myocarditis is a treatable condition which usually responds to corticosteroids and other immunosuppressive treatment (237, 238), but if it remains unrecognized, it may result in irreversible and potentially fatal consequences. The worst-case scenario occurs when the myocarditis is severe and/or fulminant leading to ventricular fibrillation which may end with cardiac arrest (239-242). Therefore, detecting the presence of myocarditis is necessary to timely initiate intensive immunosuppressive treatment as well as targeted cardiac medications. Dieval and colleagues reported that 75% of patients with ASyS and cardiac involvement recovered after treatment with immunosuppressive drugs (135).

A systematic review by Gupta *et al.* demonstrated that 38% and 22% of deaths among patients with IIM were because of myocarditis and focal myocardial fibrosis, respectively (166). Mavrogeni *et al.* performed CMR imaging in 20 patients with IIM, of whom 55% showed evidence of myocarditis. On follow-up CMR performed 3 months after corticosteroid treatment, persistent myocarditis was observed in 10 of the 12 patients (134). The study did not report the use of additional immunosuppressive drugs and myocarditis may require more intensive and prolonged treatment to achieve a therapeutic response. This may further underscore the importance of corticosteroid therapy, while also highlighting the need to combine it with other immunosuppressive agents to achieve better outcomes and prognosis.

Furthermore, it was observed by Linos and colleagues, that 20% of hospital admissions in patients with DM were associated with a concurrent atherosclerotic cardiovascular condition or intervention, and these patients had a two-fold higher risk of in-hospital mortality compared with controls and patients with DM without atherosclerotic cardiovascular disease (243).

HF represents a significant contributor to adverse outcomes in patients with IIM. Cardiac involvement, including myocarditis, ischaemic cardiovascular disease, and cardiomyopathy, may lead to progressive ventricular dysfunction and ultimately HF, which has been consistently associated with increased morbidity and mortality. Several studies have demonstrated that reduced LVEF and clinical HF are strong predictors of poor prognosis in IIM, highlighting the importance of early detection and monitoring of cardiac involvement in this patient population.

The Heart Failure Association (HFA) of European Society of Cardiology (ESC) developed a diagnostic score to evaluate the probability of HF with preserved EF, named as HFA-PEFF score. Hu and colleagues observed that among 134 patients with IIM, 22 patients (16.4%) exhibited a high HFA-PEFF score, and these patients also demonstrated a markedly reduced 5-year survival (47.1%) compared with IIM patient group with lower HFA-PEFF score (244). Dong *et al.* identified a subgroup of IIM patients with cardiac involvement in whom HF was the primary cause of death (227). Liu *et al.* observed that patients with IIM and HF exhibited a high rate of rehospitalization and increased mortality, often due to cardiovascular causes (245).

6 CARDIOVASCULAR INVESTIGATIONS IN IIM

Currently, there is a lack of up-to-date, structured recommendations for cardiological investigations in the literature and clinical practice for patients with IIM. This is one of the major causes for the underdiagnosis and delayed treatment of cardiac involvement in patients with IIM. At present, a variety of investigative methods are used to diagnose the cardiac involvement in IIM, including both invasive and non-invasive techniques.

6.1 ELECTROCARDIOGRAPHY (ECG)

ECG is considered the first-line investigative method in patients with clinically suspected cardiac involvement. ECG is a diagnostic modality that can aid in the detection of arrhythmias, conduction system abnormalities, abnormal Q waves, and/or ST–T segment changes. The frequency of abnormal ECG findings in patients with IIM ranges between 24 to 85%; however, most of the ECG findings in patients with IIM are unspecific (246). At 1993, Taylor *et al.* observed various ECG findings in 85% of 26 prospectively recruited PM patients (247), and the most frequently observed abnormalities considered of non-specific ST- and T-wave changes. Benbassat *et al.* found different types of ECG changes including non-specific ST-T changes and rhythm-conductions disorders in about 31.5% among 92 patients with PM/DM (248). Opinc *et al.* conducted a comprehensive literature review and reported that non-specific ST-T or T-wave abnormalities were the most frequently observed ECG changes, with a prevalence ranging from 12,5% to 64% of IIM cases (123).

Different types of conduction abnormalities and arrhythmias have been observed in patients with IIM (123, 169, 249). Stern *et al.* found in 1984 that heart block was the most common of ECG abnormalities in IIM, and sudden

death happened in some of these patients (250). Diederichsen *et al.* observed supraventricular arrhythmias in 36% of patients with newly diagnosed, untreated IIM (251). Significantly more frequent supraventricular tachyarrhythmias, longer QRS and QTc intervals were detected by ECG in a cohort of 76 patients with IIM (185). Liu *et al.* retrospectively evaluated ECG data from 62 patients with IIM and found that atrial and ventricular arrhythmias were present in 26% and 39% of patients, respectively (142). Liu also studied retrospectively ECG data in 52 IIM patients with chronic myocarditis and found a high proportion of ECG abnormalities, including atrial and ventricular arrhythmias as well as Q-wave abnormalities. After a median follow-up time of 2 years, a total of 22 deaths were recorded, including 20 of cardiogenic origin. Low-voltage limb leads and Q-wave abnormalities were among the variables significantly associated with poorer survival (252).

In IIM patients in our cross-sectional study (**paper I**), the presence of arrhythmias and negative T-waves was significantly more frequent among patients with established IIM compared with healthy controls, whereas in newly diagnosed IIM (**paper II)**, only ST-T changes were significantly more frequent.

6.2 TRANSTHORACIC ECHOCARDIOGRAPHY (TTE)

TTE is an ultrasound-based, non-invasive imaging technique that allows visualization of the structure and function of the heart. In IIM, TTE is used for the diagnosis of cardiac involvement and the most common echocardiographic findings reported in IIM include HF, cardiomyopathy, pericardial effusion and pulmonary hypertension (123, 196). As previously stated, the HF is initially evaluated by measuring LVEF and assessing diastolic function. However, early and subtle impairments in LVEF or diastolic function are not always

reliably detected by conventional TTE. Therefore, if LVEF and diastolic function are not impaired, further assessment of myocardial deformation using GLS, assessed by speckle-tracking echocardiography, may represent a more sensitive approach for detecting subclinical cardiac involvement in patients with IIM (129, 253). Machado *et al.* analyzed TTE data from 61 patients with IIM and 32 healthy controls (214). They observed that assessing left ventricular GLS values was a useful method to evaluate heart function, as these GLS values were significantly lower in patients with IIM than healthy controls. However, neither LVEF values nor the frequency of diastolic dysfunction showed significant differences between these two groups (214). Similar results were observed in other studies (191, 254). Serial TTE in patients with IIM may be particularly useful for the longitudinal follow-up of those with cardiac involvement, as prospective studies have demonstrated that echocardiographic parameters such as GLS are associated with disease activity and clinical outcomes over time (214).

6.3 CARDIAC MAGNETIC RESONANCE (CMR)

CMR is a non-invasive, radiation-free imaging technique of the heart that aids in the assessment of impaired heart function, chamber size changes, myocardial and/or pericardial inflammation and fibrosis. Additionally, CMR allows quantification of the extent and severity of the cardiac muscle involvement and can differentiate between ischaemic and non-ischaemic heart involvement. Subendocardial changes are typical for patients with ischaemic heart disease while mid-wall/subepicardial changes are typical for patients with non-ischaemic inflammation (103).

The main usefulness of using CMR in IIM is its ability to early detect cardiac inflammation, particularly myocarditis and pericarditis, as well as myocardial

fibrosis (196). The diagnosis of myocarditis should be based on the updated Lake Louise Criteria, incorporating T1- and T2-based tissue characterization techniques (255). Thus, CMR is highly recommended by ESC and the American College of Cardiology (ACC) in patients with suspected myocarditis (94, 255).

CMR is superior to TTE in detecting inflammation and fibrosis by using different techniques that enable detection of oedema, hyperaemia/capillary leak and necrosis (Table 4). Furthermore, CMR is able to detect both focal and global changes (255, 256). Markousis-Manrogenis and colleagues prospectively evaluated 28 patients with IIM and 20 healthy controls by CMR according to updated Lake Louise criteria. All patients exhibited cardiovascular symptoms but normal TTE findings. Approximately 96% of patients with inflammatory myopathies exhibited CMR changes consistent with acute myocarditis while none of healthy controls met any of myocarditis criteria. Furthermore, LVEF levels were significantly lower in patients in comparison to healthy controls (137). Huang *et al.* used CMR to screen for early cardiac involvement in patients with IIM and found that 30 of 49 (61%) demonstrated abnormal CMR findings. However, only 18% of these 30 patients had abnormal TTE (257).

Similar to TTE, CMR has the ability to assess cardiac function by measuring LVEF and GLS. Kersten *et al.* studied cardiac involvement in 47 patients with IIM and 25 healthy controls by using CMR. IIM patients exhibited significantly lower GLS than healthy controls. Furthermore, IIM patients with CMR evidence of myocardial fibrosis, as detected by positive late gadolinium enhancement (LGE), exhibited significantly lower LVEF and GLS compared with IIM patients with negative LGE (258). Yurchenko *et al.* evaluated CMR finding in 55 patients with established, stable IIM and 19 healthy controls, and

found that IIM patients exhibited significantly poorer heart functional parameters and higher native T1 values when compared to the healthy controls (259).

Table 4. Comparison of cardiac magnetic resonance (CMR) and transthoracic echocardiography (TTE) in cardiac assessment.

	CMR	**TTE**
Non-invasive	++	++
Availability	Limited, requires specialized equipment	Widely available, can be performed bedside
Cost	High	Low
Examination time	30–60 minutes	10–30 minutes
Quality	Very high, but limited in severe arrhythmia	Good
Evaluation of cardiac function (EF, volumes)	Gold standard, highly accurate	Good, but operator-dependent
Perform tissue characterization (fibrosis, inflammation, eodema)	Excellent	Limited
Detection of myocarditis/fibrosis	Very high sensitivity	Limited
Differentiation between ischaemic and non-ischaemic myocarditis	Very high sensitivity	Limited
Detection of pericardial inflammation	Very high sensitivity	Limited
Valve assessment	Possible	First-line method
Hemodynamic assessment	Limited	Excellent (Doppler-based)
Contraindications	Certain implanted devices, claustrophobia, renal failure, contrast allergy	Highly suitable

In our cross-sectional study (**paper I)**, 14 patients (13%) had a previous history of IIM-related cardiac involvement, and 13 patients had undergone CMR during the disease course. However, the imaging protocol followed local clinical routines and was not specifically designed to fulfill the Lake Louise criteria for myocarditis assessment.

In our cohort of newly diagnosed IIM patients (**paper II)**, CMR was performed according to updated Lake Louise criteria from 2018 in 34 patients. Sixteen patients exhibited changes of acute myocarditis/perimyocarditis, pericarditis or previous myocarditis. Noteworthy, the time between treatment start and CMR assessment was significantly longer in patients with previous myocarditis in comparison to patients with ongoing myocarditis. LVEF as assessed by CMR did not differ significantly between IIM patients with and without cardiac involvement. CMR was a more sensitive assessment method than TTE for detecting ongoing myocarditis/pericarditis and fibrosis.

6.4 POSITRON EMISSION TOMOGRAPHY (PET)

PET is an imaging technique based on the detection of positron-emitting radioactive tracers that reflect metabolic or molecular activity in tissues. The most commonly used tracer is Fluorodeoxyglucose F18 (^{18}F-FDG) and Gallium-68 DOTATOC. PET imaging is widely used to detect malignancy and inflammation. In rheumatic diseases, such as vasculitis and IIM, PET can detect inflammation by visualizing increased glucose metabolism in activated inflammatory cells (260, 261). In patients with suspected myocarditis, PET imaging may be used as a complementary tool alongside other imaging techniques to identify myocardial inflammation (262).

In patients with cardiac sarcoidosis, PET imaging may be helpful in predicting adverse cardiac consequences such as ventricular arrhythmias, heart failure, and sudden cardiac death (263). Several studies have shown that PET imaging is a highly sensitive technique to detect immune checkpoint inhibitor-related myocarditis (264, 265).

In IIM, the primary application of PET imaging has been the detection of malignancy rather than detecting cardiac inflammation, partly because of limited availability, need of dietary preparation and high costs (266, 267).

Regarding the detection of cardiac involvement by PET in IIM, the available evidence seems to be limited. Polte *et al.* reported a case of an18-year-old man with newly diagnosed IIM exhibiting elevated cardiac troponin I levels and frequent premature ventricular arrhythmias. CMR showed signs of myocardial inflammation, which were confirmed by PET imaging (240).

6.5 ENDOMYOCARDIAL BIOPSY

Endomyocardial biopsy remains a valuable diagnostic tool in cases where the diagnosis of myocardial involvement is uncertain. It allows for direct histopathological assessment of myocardial tissue, enabling the identification of inflammatory infiltrates, myocyte necrosis, and fibrosis, as well as characterization of the underlying pathological pattern. This is particularly important for distinguishing between different forms of myocarditis and other cardiomyopathies. Despite being an invasive procedure with limited sensitivity related to sampling error, endomyocardial biopsy is regarded as the definitive diagnostic method for the diagnosis of myocarditis, especially in clinically ambiguous or severe cases (94, 268). Because of the patchy nature of myocarditis in IIM, there is a potential risk that these changes may not be captured during biopsy.

Denbow *et al.* conducted a clinicopathologic study of 20 autopsied patients with PM to evaluate the extent and nature of cardiac involvement. Histological examination revealed myocardial inflammation, myocyte necrosis, interstitial fibrosis, and, in some cases, vascular changes. Involvement of the cardiac conduction system was also observed, providing a structural explanation for arrhythmias and conduction abnormalities seen clinically (131). Haupt *et al.* investigated cardiac involvement in PM and DM through clinicopathologic evaluation of 16 autopsied patients. Histopathological analysis revealed frequent myocardial involvement, including inflammatory infiltrates, myocyte necrosis, fibrosis, and fatty replacement. The cardiac conduction system was also commonly affected, with evidence of inflammation and fibrosis. Many patients had minimal or no cardiac symptoms during life despite significant pathological findings at autopsy, highlighting the subclinical nature of cardiac involvement in IIM (130).

6.6 CARDIAC BIOMARKERS

6.6.1 CARDIAC TROPONIN I (CTNI)

Cardiac troponin I and T (cTnI and cTnT) are serum biomarkers generally associated with cardiovascular involvement, both ischaemic and non-ischaemic myocardial injury (269, 270). Currently used high-sensitivity cardiac troponin assays show superior analytical precision with high reliability for early detection of myocardial infarction (271). cTnI is a highly specific biomarker of cardiac muscle involvement, and the levels of cTnI are highly influenced by myocardial disorders (272, 273). On the other hand, cTnT is less cardiac-specific than cTnI, since its levels can be affected by non-cardiac diseases, such as musculoskeletal diseases and renal failure (274, 275). patients with IIM frequently exhibit elevated cTnT levels, which are often related to ongoing skeletal muscle regeneration rather than myocardial injury. Thus,

when cardiac involvement is suspected in patients with IIM, measurement of cTnI is recommended as the primary biomarker to help confirm myocardial involvement (276). Lilleker *et al.* investigated the differential predictive value of cTnT and cTnI in IIM patients and found that both biomarkers were associated with increased disease activity, whereas only cTnI predicted cardiac involvement (277). Zhang *et al.* analyzed the value of cTnI in 142 patients with IIM and found that elevated high-sensitivity cTnI showed the highest area under the curve for identifying cardiac involvement (278). Liu *et al.* examined the clinical characteristics of IIM patients with myocarditis compared with IIM patients without myocarditis. They found that cTnI levels were significantly higher in patients with myocarditis in comparison to those without myocarditis (142). Nevertheless, despite its superior cardiac specificity, access to cTnI assays remains limited in many healthcare centers globally, which may hamper its implementation as a screening tool for cardiac involvement in patients with IIM.

In **paper I**, we found significantly higher cTnI levels observed in IIM patients with previous history of clinical cardiac involvement in comparison to those without previous cardiac involvement and healthy controls.

In **paper II,** we reported that IIM patients with ongoing myocarditis/perimyocarditis exhibited significantly higher cTnI levels at early disease onset compared with those with ongoing pericarditis or previous myocarditis. These findings suggest that cTnI may serve as a useful biomarker for identifying active myocardial involvement in IIM and may help distinguish ongoing myocarditis from other forms of cardiac involvement.

6.6.2 N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE (NT-PROBNP)

NT-proBNP is a hormone belonging to the natriuretic peptide group, which plays an important role in inducing hemodynamic and anti-remodeling processes in the cardiovascular system (279, 280). NT-proBNP is released primarily from the heart, particularly from ventricles, and its concentration increases in conditions that lead to cardiac overload or damage (279, 281). NT-proBNP is considered one of the most important diagnostics markers in heart diseases, specifically in heart failure (282-284). According to ESC, in individuals with symptoms suggestive of HF, measurement of NT-proBNP levels should be the initial step to guide further cardiac evaluation (179). In cases where NT-proBNP levels are above 125 ng/L together with symptoms of HF, it is reasonable to further investigate these individuals with ECG and TTE. Furthermore, NT-proBNP plays an important role both in predicting prognosis and guiding the management of the HF and other cardiovascular conditions (284, 285).

In IIM, NT-proBNP levels, as in general population, may correlate to several cardiovascular disorders. Dong *et al.* conducted a retrospective study including 88 patients with IIM and cardiac involvement. They observed that IIM patients with severe cardiac damage exhibited significantly lower LVEF and higher NT-proBNP levels compared to IIM patients with milder cardiac involvement and normal LVEF (227). Liu *et al.* conducted a single-center retrospective study analyzing different clinical and laboratory data in IIM patients with and without myocarditis (142). The IIM patient cohort with myocarditis demonstrated significantly more frequent echocardiographic findings of HF, including low LVEF and diastolic dysfunction, as well as higher NT-proBNP levels compared to those without myocarditis (142). In a prospective observational study including 25 patients with established PM/DM, the

presence of subclinical myocardial fibrosis, detected by CMR, was positively associated with NT-proBNP levels (286). Similar results were observed in another study including 44 patients with newly diagnosed IIM (238). These findings suggest that myocardial inflammation/fibrosis in IIM patients is associated with a higher burden of cardiac dysfunction and that elevated NT-proBNP may serve as a useful biomarker for identifying HF-related cardiac involvement in this patient population.

A potential limitation of NT-proBNP as a biomarker in IIM is that elevated levels may reflect pre-existing cardiac disease rather than cardiac involvement directly related to IIM. Patients with IIM are often older and may have pre-existing cardiovascular conditions, including heart failure, ischaemic heart disease, or hypertension, all of which can increase NT-proBNP levels independently of myocardial inflammation. Therefore, elevated NT-proBNP should be interpreted with caution and in the context of the patient's overall clinical presentation. A careful medical history and assessment of pre-existing cardiac conditions are essential to determine whether elevated NT-proBNP levels are likely related to active cardiac involvement in IIM.

In **paper I**, we reported that significantly higher NT-proBNP levels as well as more frequent elevated NT-proBNP values were observed in patients with established IIM compared to healthy controls.

In **paper II**, we described significantly higher NT-proBNP levels among newly diagnosed IIM patients compared to healthy controls. NT-proBNP levels were higher among IIM patients with ongoing myocarditis/perimyocarditis than pericarditis and previous myocarditis; however, the difference did not reach statistical significance.

6.6.3 SOLUBLE SUPPRESSION OF TUMORIGENICITY 2 (SST2)

Soluble suppression of tumorigenicity (sST2) is a protein belonging to an interleukin-1 (IL-1) receptor family and released in response to stress on tissues such as cardiovascular diseases, pulmonary diseases, sepsis and trauma (287-289). sST2 is a part of the ST2/IL-33 pathway, which is a biomechanical signaling system that includes 3 biomarkers belonging to IL-1 family (290). These 3 biomarkers are: interleukin-33 (IL-33) and 2 different isoforms of suppression of tumorigenicity 2 receptor – soluble form (sST2) and transmembrane form (ST2L) (291). Binding between ST2L and IL-33 promote a cardioprotective mechanism while binding between sST2 and IL-33 tends to inhibit this signal (292, 293). Consequently, elevated circulating levels of sST2 may disrupt the cardioprotective pathway (ST2L/IL-33 system), thereby attenuate its protective effects and promoting myocardial hypertrophy and fibrosis (294) (Figure 2).

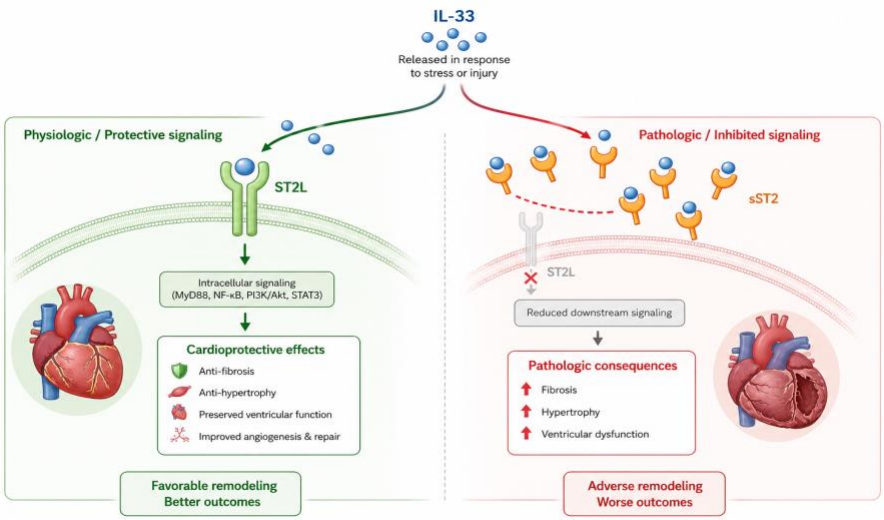

Figure 2. Binding between IL-33 and sST2 blocking the cardioprotective signaling that may have occurred through IL-33 and ST2L binding.

More than two decades ago, it was observed that sST2 levels were elevated in patients with severe HF and were positively correlated with natriuretic peptide concentrations (287). Zhang *et al.* performed a systematic review and meta-analysis to study the diagnostic value of sST2 in patients with cardiovascular diseases and concluded that sST2 levels were significantly associated with HF, while no significant association was found with ischemic heart diseases or myocardial infarction (295).

Furthermore, sST2 has been found to be a strong predictor of poor cardiac outcomes and used as a prognostic marker together with NT-proBNP for stratifying the prognostic outcome in patients with heart diseases (296-298). Tang *et al.* demonstrated that patients with acute HF exhibited increased sST2 levels and higher sST2 levels at baseline, 48 hours and 72 hours were associated with increased risk of death or rehospitalization during next 30 days, suggesting that sST2 could predict poor outcomes in acute HF (299). Tyminska *et al.* performed a prospective observational study of 117 patients experiencing their first-time ST-elevation myocardial infarction (STEMI) managed with primary percutan coronary intervention (PCI) (300). sST2 levels were measured at baseline, and 104 patients were followed for 1 year. Baseline sST2 levels were associated with a more severe clinical presentation and were predictive of cardiovascular death or hospitalization for HF during the one-year follow-up period (300).

However, the role of sST2 in rheumatic diseases in general, and particularly in IIM with cardiac involvement, has been studied in a limited extent. For instance, elevated sST2 levels have been reported in patients with RA, where they were associated with disease activity and systemic inflammation (301, 302). Similarly, increased circulating sST2 concentrations have been described in SLE, where they may reflect immune activation and organ involvement

(303, 304). In systemic sclerosis, sST2 levels have been linked to disease activity, myocardial fibrosis and cardiac dysfunction, suggesting a potential role as a biomarker of cardiovascular involvement (305, 306).

Yuan *et al*. studied sST2 blood levels in a cross-sectional study of 70 patients with PM or DM. sST2 levels were significantly higher in those patients compared to healthy controls. Furthermore, sST2 levels were significantly correlated to IIM disease activity parameters such as C-reactive protein (CRP), CK, LDH and visual analogue scales score. However, information regarding the presence of cardiac involvement in this patient cohort was not available (307). Similarly, in a Polish single-centre study, sST2 levels were significantly higher in IIM patients than in healthy controls (308). Moreover, sST2 levels were significantly higher in patients who were positive for anti-SRP antibodies than in those who were anti-SRP-negative. In addition, median levels of NT-proBNP in the IIM cohort exceeded the normal reference range and 24 hours ECG holter monitoring revealed presence of arrhythmias in some patients, suggesting a possible degree of subclinical cardiac involvement. The authors observed no correlation between sST2 levels and cardiac symptoms or cardiac biomarkers such as NT-proBNP and cTnI. Interpretation of these findings is limited by the absence of systematic cardiac imaging, as neither TTE nor CMR imaging was performed (308).

Sun *et al.* studied the diagnostic value of sST2 in 44 IIM patients with normal heart function and no previous history of cardiovascular disease or myocarditis. All patients were examined by CMR. The study demonstrated that sST2 levels were significantly higher in IIM patients compared with healthy controls. Furthermore, sST2 levels were significantly higher in IIM patients with myocardial fibrosis, either diffuse or focal, as evaluated by CMR, than in

IIM patients without myocardial fibrosis, suggesting that sST2 levels may predict subclinical cardiac involvement in IIM (294).

Li *et al.* evaluated the diagnostic utility of sST2 for detecting cardiac involvement in IIM. Cardiac involvement was defined based on ECG and/or echocardiographic abnormalities. They observed that IIM patients with cardiac involvement had significantly higher sST2 levels than those without cardiac involvement, and elevated sST2 levels were identified as a risk factor for cardiac involvement in IIM (309).

In **paper III**, we reported that patients with newly diagnosed IIM with ongoing myocarditis/pericarditis had significantly higher sST2 levels than patients without cardiac involvement and RA controls. Additionally, sST2 levels were associated with cTnI, NT-proBNP, and CMR signs of cardiac inflammation (310).

7 METHODOLOGY AND RESULTS

7.1 PAPER I

The study was a single-centre, cross-sectional, case-control study in which patients with IIM who followed at the Department of Rheumatology, Sahlgrenska University Hospital, were identified from registries during the period from August 2020 to August 2022, using the International Classification of Diseases, 10th Revision (ICD-10) codes M33.2, M60.9, M33.9 and M33.1. Out of 180 IIM patients, 109 patients were included in the study (Figure 3). Further detailed information about inclusion and exclusion criteria is found in the paper I.

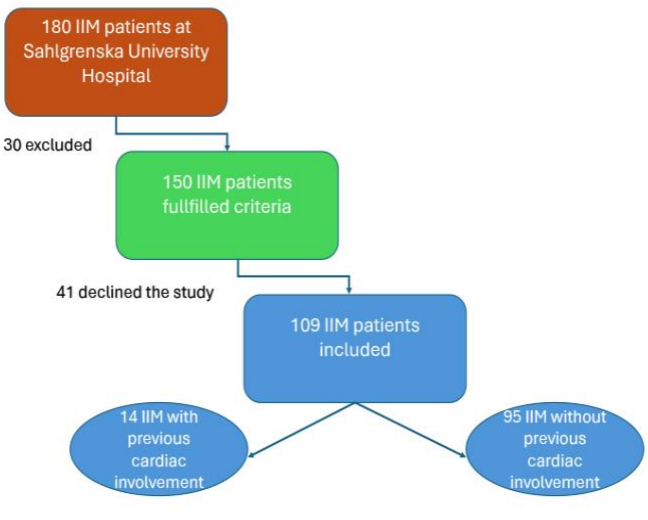

Figure 3. Flowchart of patient inclusion in the paper I.

The control group, matched for age and sex, consisted of 20 healthy individuals without autoimmune rheumatic diseases, and was predominantly recruited from hospital staff and research staff. The controls were allowed to have diabetes mellitus, hypertension, and dyslipidaemia, but were not allowed to have previous history of ischaemic heart disease, HF, or severe renal failure during the 12 months prior to inclusion.

A face-to-face interview was conducted by the author with each patient and healthy control, and written informed consent was obtained from each participant. Information regarding current medications, cardiovascular risk factors and events, and standardized Health Assessment Questionnaire-Disability Index (HAQ-DI) was collected from patients and controls. Additionally, disease activity and damage were evaluated according to the core set measures of the International Myositis Assessment & Clinical Studies Groups (IMACS) (311).

Following the interview, blood pressure, heart rate, body weight and height were measured, and ECG recordings and blood samples were obtained from each participant by a research nurse. All participants were referred for TTE.

The main results of paper I were:

1. Patients with IIM had a significantly higher prevalence of traditional cardiovascular risk factors, such as obesity, diabetes mellitus, and dyslipidemia compared to healthy controls.
2. A significantly higher proportion of IIM patients had a pathological NT-proBNP value (>125 ng/L) compared with healthy controls (40% vs 10%, P=0.010).
3. Abnormal ECG findings were observed in 48 IIM patients (44%) which were significantly higher than in healthy controls (44% vs 15%,

P=0.023). There were notable variations in the presence of arrhythmia, cardiac axis deviation, and the occurrence of negative T waves.

4. Thirteen percent of IIM patients (n=14) had previous clinically evident cardiac involvement, with IMNM representing the predominant subgroup among these patients (n=7, 50%) with following antibody profile: 2 with positive anti-HMGCR, 1 with positive anti-SRP, 1 with positive anti-PM/Scl75 and 3 with negative MSA/MAA.
5. IIM patients with previous clinical cardiac involvement exhibited significantly higher levels of NT-proBNP, cTnI, and higher frequency of suspected PH compared to healthy controls.

7.2 PAPER II

In this prospective, single-centre study, we identified 75 patients with newly diagnosed IIM during the period from February 2020 to September 2022. Of these, 47 patients met the eligibility criteria, and 40 patients consented to participate in the study. Twenty healthy controls, matched for age and sex, were recruited. A face-to-face interview was conducted by the author with each patient and healthy control, and written informed consent was obtained from each participant. Following the interview, blood pressure, heart rate, body weight and height were measured, and ECG recordings and blood samples were obtained from each participant by a research nurse. Finally, 34 patients and 9 healthy controls who underwent ECG, TTE and CMR were included in the analysis (Figure 4). Further detailed information regarding inclusion and exclusion criteria, clinical and laboratory data collection is provided in paper II.

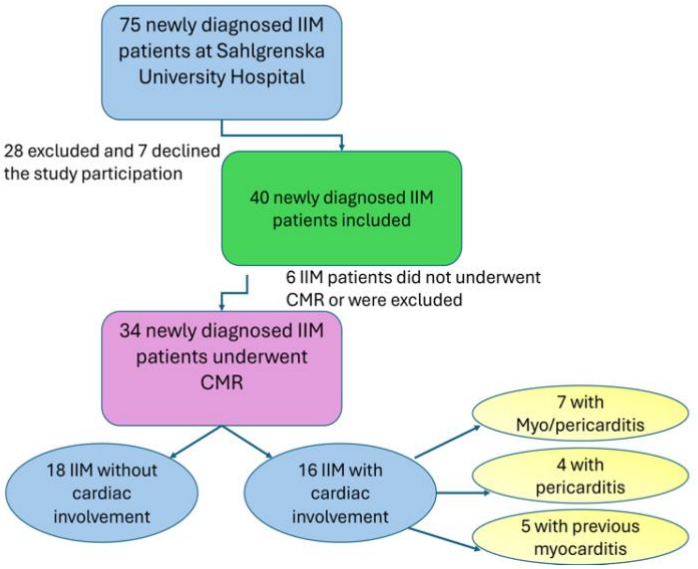

Figure 4. Flowchart of patient inclusion in the paper II.

The main results of paper II were:

1. The occurrence of myocardial pathology on CMR was significantly more frequent in patients with IIM than in healthy controls (P=0.016, Table 5). Sixteen IIM patients (47%) exhibited cardiac involvement with pathological changes on CMR indicating myocarditis/perimyocarditis (n=7), pericarditis (n=4), or previous myocarditis (n=5).
2. In the IIM patient group with cardiac involvement, 44% (n=7) had IMNM, 4 of whom had positive anti-HMGCR antibodies). In the patient group without cardiac involvement, ASyS was the most common subtype (n=8, 44.5%).
3. IIM patients with cardiac involvement exhibited significantly increased serum levels of muscle enzymes (AST and ALT), together with a higher prevalence of clinical myositis and elevated CK concentrations, compared with those without cardiac involvement.

Table 5. Overview of CMR findings in newly diagnosed IIM and healthy controls.

IIM (n=34)	Controls (n=9)	*P*-value
CMR sign of cardiac involvement, n (%), 16 (47)	0	**0.016**
- Acute myocarditis/perimyocarditis, 7 (21)		
- Acute pericarditis, 4 (12)		
- Previous myocarditis/perimyocarditis, 5 (15)		
No CMR sign of cardiac involvement, n (%), 18 (53)	0	ns

4. Serum levels of cTnI and the frequency of elevated cTnI were significantly higher in IIM patients with myocarditis/perimyocarditis compared to IIM patients with pericarditis and previous myocarditis. Additionally, serum levels of myoglobin were significantly higher in IIM patient group with myocarditis/perimyocarditis than patient group with previous myocarditis.
5. cTnI levels were significantly positively correlated to muscle disease activity indicators such as serum levels of muscle enzymes (CK, LDH, and AST), the presence of clinical myositis, physician global assessment of disease activity and prednisolone dose. Furthermore, cTnI levels were significantly positively correlated to NT-proBNP levels, the presence of ST-T changes and CMR findings indicating myocarditis/perimyocarditis.
6. Out of 16 IIM patients with cardiac involvement, 3 patients were identified as having severe cardiac involvement based on cTnI > 288

ng/L. All 3 patients were male and presented with clinical myositis. Two had IMNM and exhibited life-threatening arrhythmias and manifestations of HF, including pathologic EF, GLS EDVI and ESVI.

7.3 PAPER III

This was a single-centre study aimed to investigate the role of sST2 in IIM and its potential association with cardiac involvement in the disease. Two IIM patient cohorts, one RA patient cohort, and 89 healthy controls were included in this study. The prospective IIM cohort consisted of 34 newly diagnosed patients with IIM who were prospectively followed up at 6, 12 and 24 months. The cross-sectional cohort included 109 patients with established IIM identified from patient registries between 2003 and 2022; all diagnosed at least 6 months before inclusion. The detailed information about these 2 IIM patient cohorts regarding inclusion and exclusion criteria, data collection, cardiac investigation, and laboratory results are reported in paper I and II. The RA patient cohort consisted of 32 patients with newly diagnosed RA who were positive for rheumatoid factor and/or anti-citrullinated protein antibody, had active disease, and were naive to disease-modifying antirheumatic drugs. These patients were matched to the prospective IIM cohort with respect to age and sex. The healthy control group consisted of age- and sex-matched individuals recruited to the prospective IIM study plus additional blood donors.

Serum sST2 concentrations were measured in all three patient cohorts and in healthy controls. In the prospective cohort of newly diagnosed IIM patients, sST2 levels were assessed longitudinally at four predefined study visits over a 2-year follow-up period. Further details regarding the study methodology are provided in paper III.

The main results of paper III were:

1. Patients with newly diagnosed IIM exhibited significantly higher median serum sST2 levels than patients with established disease from the cross-sectional cohort and healthy control subjects.
2. In patients with newly diagnosed IIM, median sST2 levels were significantly higher at baseline compared with levels measured at 6, 12, and 24 months.
3. Significantly higher sST2 concentrations were observed in newly diagnosed IIM patients with ongoing myocarditis and/or pericarditis than in patients without evidence of active myocarditis/perimyocarditis and in patients with active RA.
4. Baseline sST2 levels were positively associated with cTnI, NT-proBNP and signs of ongoing cardiac inflammation on CMR.
5. sST2 levels in IIM patients with established disease were positively associated with cardiovascular risk factors.

7.4 PAPER IV

The study was conducted to investigate and follow up cardiac involvement in patients with IIM over time. Myositis disease activity measures, cardiac biomarkers, and cardiac assessments (ECG and TTE) were repeatedly evaluated at baseline and at 6-, 12-, and 24-month for 34 IIM patients. CMR imaging was performed for 34 patients at baseline and 13 patients at 24 months. Further details regarding the study methodology are provided in Paper IV.

At 24 months, myositis disease activity was lower than at baseline. cTnI also decreased significantly, while NT-proBNP did not. Cardiovascular comorbidities were unchanged, and fibrotic CMR findings persisted. Severe cardiac involvement was associated with worse myocardial function than mild-to-moderate involvement. More detailed results can be found in paper IV.

8 DISCUSSION

This thesis aims to broaden our understanding of the clinical presentation of cardiac involvement in IIM. As early as 1977, cardiac involvement in IIM was recognized as relatively common, with an estimated prevalence of approximately 35–38% (124, 312). These early observations highlighted that cardiac manifestations are not rare in IIM and may represent an essential component of the disease rather than an incidental finding. The reported prevalence of cardiac involvement in patients with IIM varied depending on study type, patient selection and applied diagnostic methods. Subsequent studies have further demonstrated that cardiac involvement encompasses a broad spectrum, ranging from subclinical abnormalities to clinically overt conditions such as myocarditis, arrhythmias, and heart failure. When reviewed systematically, patients with IIM exhibit a significantly increased risk for cardiac morbidity and mortality.

A variety of mechanisms and contributing factors are involved in the development of cardiac involvement in patients with IIM (figure 5). Direct inflammatory infiltration of the myocardium may lead to conditions such as myocarditis, pericarditis, or perimyocarditis, reflecting the underlying immune-mediated muscle injury that also affects skeletal muscle. In addition, systemic inflammation may promote endothelial dysfunction, accelerated atherosclerosis, and microvascular damage. Furthermore, long-term immunosuppressive therapy, particularly glucocorticoids, may contribute to an increased burden of traditional cardiovascular risk factors, including hypertension, dyslipidemia, and insulin resistance (313, 314). Collectively, these mechanisms likely explain the increased prevalence of both inflammatory and non-inflammatory cardiovascular diseases observed in patients with IIM.

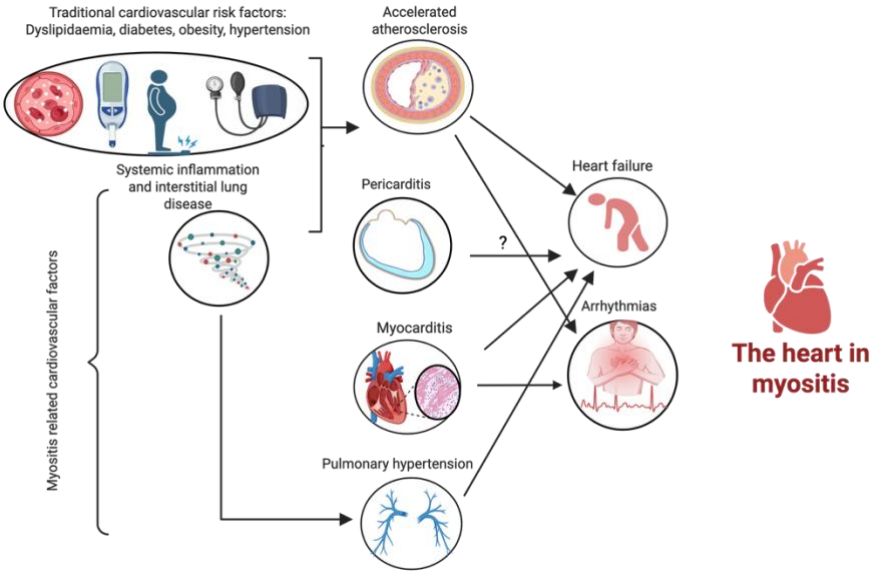

Figure 5. mechanisms and contributing factors involved in the development of cardiac involvement in IIM

In **paper I,** we demonstrated findings consistent with previous reports, showing a higher prevalence of cardiovascular risk factors in patients with IIM compared with the general population. These findings support the need for systematic screening of cardiovascular risk factors in IIM patients in order to reduce their morbidity and mortality risk.

Although myocarditis, pericarditis or perimyocarditis can occur at any timepoint in the course of disease, IIM patients in our prospective cohort (**paper II**) appeared to develop myocardial inflammation early in the course of the disease. Furthermore, the risk of relapse and long-term progression of inflammation within 24-month follow-up was low. However, this finding should be interpreted with caution, as CMR and cardiac biomarker results were made available to treating physicians for ethical reasons. Thus, anti-inflammatory therapy in some newly diagnosed IIM patients included in the

prospective study was intensified following the detection of heart involvement. Furthermore, adding anti-arrhythmic and HF therapy to these patients, as well as referral for cardiologist follow-up may otherwise not have occurred in asymptomatic patients. Consequently, treatment decisions may have been influenced by imaging and laboratory findings. Thus, the use of targeted immunosuppressive therapy may have contributed to the stabilization of myocardial inflammation over time, while adjunctive cardioprotective medications may have improved cardiac function and mitigated arrhythmias. Based on our findings, we propose that all patients with newly diagnosed IIM, particularly those with significant skeletal muscle involvement, should undergo screening for cardiac involvement using cardiac biomarkers measurement, ECG, and TTE. In patients with suspected cardiac involvement based on clinical evaluation or initial screening results, CMR should be performed to confirm the diagnosis and further characterize the extent of myocardial involvement which warrant further investigation (Figure 6; modified figure from paper II).

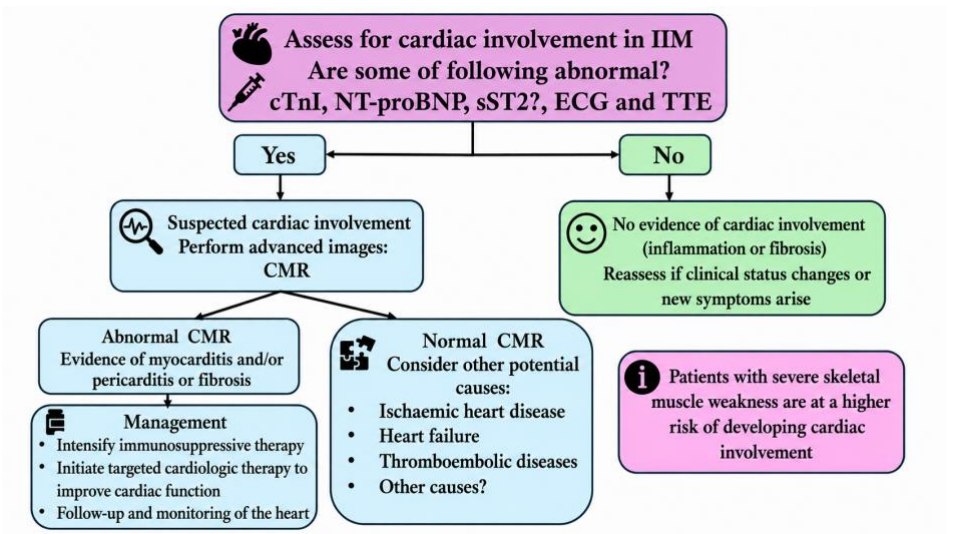

Figure 6. Proposed algorithm for screening and diagnosis of cardiac involvement in newly diagnosed IIM patients (modified from paper II).

Myocardial inflammation may lead to the development of fibrosis as a consequence of chronic injury and subsequent tissue remodeling. In our prospective longitudinal cohort (**paper IV**), out of 11 patients with cardiac involvement at baseline, 9 patients demonstrated fibrosis at the 24-month follow-up. Notably, fibrosis was evident at baseline in 8 of the 9 patients. This persistence, and slight increase, in fibrotic findings over time may reflect irreversible myocardial remodeling, suggesting that myocardial fibrotic changes in IIM may represent irreversible remodeling that remains despite ongoing immunosuppressive treatments. However, not all IIM patients included at baseline underwent follow-up CMR at the 24-month assessment due to financial constraints. This limits the ability to draw definitive conclusions regarding the true prevalence and progression of myocardial fibrosis over time. In addition, new cases of myocarditis or perimyocarditis occurring during the course of the disease may have remained undetected, potentially leading to an underestimation of cardiac involvement in the cohort.

It is well-known that skeletal and cardiac muscle share many structural and functional characteristics, reflecting their common striated muscle architecture (315). This biological similarity is particularly relevant in IIM, where pathological processes affecting skeletal muscle may also involve the myocardium (316, 317). Zhang *et al.* supports the concept that cardiac involvement in IIM is not a separate entity but rather part of the same systemic inflammatory process affecting skeletal muscle tissues (317). Dieval *et al.* observed that myocarditis was consistently associated with active myositis, along with significantly elevated levels of CK and cTnI in patients with ASyS (135). In a cohort of 57 patients with IMNM, cardiac involvement was identified in 52% of cases (219). I our patients, including both cross-sectional and prospective cohorts (**paper I** and **II**), IMNM was the most prevalent IIM subgroup with cardiac involvement. However, the number of IMNM patients

included in each cohort may have been insufficient to draw definite conclusions for this specific subgroup of IIM. Moreover, the assessment of cardiac involvement in the cross-sectional study was based on clinical evaluation and retrospective review of medical records, which introduces a risk of misclassification and the potential underdetection of subclinical cardiac involvement. Due to the high cost of CMR, this modality was not performed in the cohort; consequently, the evaluation of functional and structural cardiac abnormalities relied solely on TTE.

A key limitation of this study that warrants acknowledgment is the relatively small sample size of both patients with IIM and healthy controls, in addition to its unicentric design. This was, in part, influenced by the COVID-19 pandemic, during which restrictions and safety considerations limited patient participation, particularly due to concerns about unnecessary exposure to infection risk associated with longer travel to our study site in Gothenburg.

Additionally, in **Paper I**, we applied the older Bohan and Peter criteria rather than the EULAR/ACR classification criteria, as the dates of diagnosis for the included IIM patients preceded the availability of the newer criteria. Consequently, patient classification was based on the diagnostic standards in clinical use at the time, ensuring consistency with contemporaneous clinical practice.

9 CONCLUSION AND FUTURE PERSPECTIVES

The present thesis demonstrates that cardiac involvement in IIM is not uncommon and should be recognized as a clinically significant manifestation, given its potential impact on quality of life and mortality. Myocarditis and pericarditis emerged as among the most common forms of cardiac involvement in IIM. Our findings underscore the importance of early and accurate detection of cardiac manifestations. We demonstrated that cTnI and CMR are valuable tools for the diagnosis and evaluation of myocardial involvement, while sST2 may represent a promising biomarker for the identification and monitoring of cardiac disease in this patient population. Furthermore, the thesis provides an overview of the importance of recognizing that diverse forms of cardiac involvement may occur across the different stages of IIM (Figure 7). A comprehensive understanding of these stage-specific patterns is essential for timely detection, appropriate risk stratification, and optimized clinical management of patients with IIM.

Our aim is to continue a longitudinal follow-up of IIM patients who were enrolled at the time of diagnosis, with a planned observation period of five years. Within this cohort, we intend to assess overall survival, the incidence of cardiovascular risk factors and cardiovascular disease, the development of heart failure, as well as changes in cardiac function and structural remodeling. These outcomes will be compared between IIM patients with and without cardiac involvement. We also plan to investigate whether baseline levels of sST2 are predictive of subsequent heart failure and adverse clinical outcomes in this patient population. Specifically, we aim to evaluate the prognostic value of sST2 measured at diagnosis in relation to the development of heart failure,

disease progression, and overall prognosis. These analyses will help determine whether sST2 can serve as an early risk stratification biomarker in patients with

In addition, serum samples have been collected and stored at the baseline, and at 6, 12, and 24 months of follow-up. These samples provide a valuable opportunity for future biomarker analyses. We plan to establish collaborations with other research centres to facilitate the investigation of novel circulating markers associated with cardiac involvement in patients with IIM, with the aim of improving early detection, risk stratification, and understanding of underlying pathophysiological mechanisms.

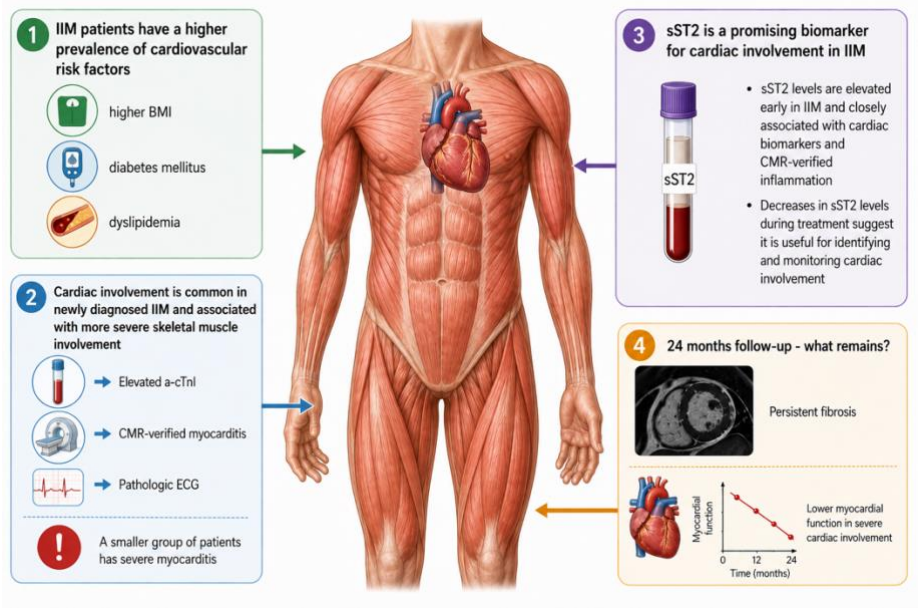

Figure 7. Summary of results from paper I-IV

USE OF GENERATIVE AI

Generative AI (ChatGPT, OpenAI) was used to assist in the design and graphical refinement of some figures included in this thesis. The scientific content, interpretation, and accuracy of all figures were reviewed and verified by the author.

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