Cardiac involvement in newly diagnosed patients with idiopathic inflammatory myopathies is associated with skeletal muscle involvement

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Abstract

Objective

Idiopathic inflammatory myopathies (IIM) can affect multiple organs, including the heart, potentially leading to arrhythmia, heart failure, and thereby a poor prognosis. We hypothesised that cardiac and skeletal muscle involvement in patients with IIM share pathological mechanisms, and that severe skeletal muscle involvement may be associated with cardiac involvement. The aim of this study was to identify disease-related parameters that indicate cardiac involvement in newly diagnosed patients with IIM.

Methods

In this prospective study, 34 newly diagnosed patients with IIM and 9 age- and gender-matched healthy controls underwent cardiac magnetic resonance imaging, blood analyses for skeletal muscle markers, and assessments of IIM-specific disease features.

Results

Cardiac involvement was detected by cardiac magnetic resonance imaging in 47% of patients with newly diagnosed IIM, presenting as ongoing myocarditis/perimyocarditis (44%), ongoing pericarditis (25%) or previous myocarditis (31%). IIM patients with cardiac involvement had significantly more prevalent myositis (p=0.018) and higher levels of serum markers of muscle inflammation (myoglobin, p=0.039; alanine aminotransferase, p=0.045 and aspartate aminotransferase p=0.005) compared to IIM without cardiac involvement. IIM with ongoing myocarditis/peri-myocarditis displayed significantly elevated cardiac troponin I (cTnI) levels than IIM with ongoing pericarditis (p=0.015) or previous myocarditis (p=0.015). Additionally, cTnI levels were strongly correlated to myositis (as clinical manifestation, p=0.011), creatin kinase (p=0.001), myoglobin (p=0.001), lactate dehydrogenase (p=0.008) and aspartate aminotransferase (p=0.0.001)

Conclusion

Cardiac involvement as detected by cardiac magnetic resonance imaging is common at time of diagnosis in patients with IIM and is closely linked to the severity of skeletal muscle involvement.

Key words

idiopathic inflammatory myopathies, cardiovascular diseases, biomarkers, magnetic resonance imaging

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Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune diseases primarily characterised by chronic skeletal muscle inflammation. Beyond skeletal muscle involvement, IIM can affect multiple organ systems, including the skin, joints, oesophagus, lungs, and heart (1, 2). Cardiac involvement in IIM may manifest as inflammatory heart disease, leading to congestive heart failure and severe arrhythmias, with clinically significance observed in approximately 9% of patients (3).

However, subclinical cardiac involvement is far more common, with an estimated prevalence of 32–76% (4, 5). While the long-term outcomes of cardiac involvement in IIM have not been extensively studied in prospective longitudinal studies, heart failure is frequently reported in these patients (6). Compared to the general population, patients with polymyositis (PM) and dermatomyositis (DM) have an increased risk to develop heart failure (hazard ratio 2.06), with the risk persisting up to 10 years post-diagnosis (7). Notably, the risk of death from cardiovascular disease was increased already in the first year after myositis diagnosis (8). Young and middle-aged patients with PM/DM exhibit a higher prevalence of arrhythmias, particularly supraventricular arrhythmias, compared to matched controls. These arrhythmias were also associated with poorer prognosis (9).

Since most cardiac involvements in IIM are asymptomatic, and symptoms, when present, are often nonspecific, early detection relies on cardiac biomarkers and imaging techniques. Cardiac troponin I (cTnI) is more specific for myocardial damage than cardiac troponin T that can also arise from skeletal muscle inflammation or damage (10, 11). Elevated cTnI has shown high specificity and positive predictive value for cardiac involvement, particularly in patients with myocarditis (12, 14). However, cTnI is not available in many centres, limiting its use. Imaging technology such as cardiac magnetic resonance (CMR) is the current non-invasive reference standard for establishing the diagnosis of myocarditis based on the updated Lake Louise Criteria (15). Using CMR myocardial inflammation was detected in up to 62% of patients with newly diagnosed IIM, however, no controls were included (16). In contrast, findings from electrocardiography and transthoracic echocardiography are often non-specific (17).

Autopsy studies have revealed that the histopathological features of myocarditis in IIM resemble those of skeletal muscle inflammation (18). This suggests a common underlying disease mechanism for both skeletal and cardiac muscle involvement. To test this hypothesis, we have investigated prospectively a cohort of newly diagnosed patients with IIM, all of whom underwent standardised CMR protocols to assess cardiac involvement. Age- and sex-matched healthy controls were also included. Disease-related parameters were compared between patients with and without CMR-verified cardiac involvement, with a particular focus on the relationship between skeletal muscle parameters and cardiac involvement.

Patients and methods

Patients and healthy controls

This is a prospective, single-centre study in which 75 patients with newly diagnosed IIM were recruited at the Rheumatology Clinic, Sahlgrenska University Hospital in Gothenburg, Sweden, between February 2020 to September 2022. Patients were included if they were adults (≥18 years) and met the 2017 EULAR/ACR classification criteria for IIM (19) or fulfilled Connors' criteria for anti-synthetase syndrome (ASyS) (20) or criteria for overlap myositis (21). Patients were classified using a scoring system according to 2017 EULAR/ACR criteria: definite IIM (total score ≥7.5 without and ≥8.7 with muscle biopsy), probable IIM (≥5.5 without and ≥6.7 with biopsy), and possible IIM (≥5.3 without and ≥6.5 with biopsy). Exclusion criteria were a diagnosis of inclusion body myositis, age over 80 years, severe heart failure diagnosed within the past 12 months, and initiation of treatment for IIM more than two months prior to

enrolment. Out of the 75 identified patients, 47 were eligible and 40 agreed to participate in the study. Patients unable to undergo CMR investigations due to medical or other reasons were excluded. Ultimately, 34 patients were included, ten patients (29%) were classified to have definite IIM (3 immune-mediated necrotising myositis (IMNM), 3 ASyS, 2 DM and 2 overlap myositis), 15 patients (44%) had probable (6 IMNM, 4 ASyS, 4 DM and 1 overlap myositis) and four patients (12%) possible IIM (2 IMNM, 1 ASyS and 1 DM) according to 2017 EULAR/ACR classification criteria. The remaining patients (15%) with available biopsy results did not reach the ≥6.5 points threshold. They fulfilled the criteria for ASyS (n=2) or were diagnosed as clinical and biopsy-verified IMNM (n=2), and polymyositis (n=1), according to Bohan and Peters diagnostic criteria. An overview of the study design can be found in Supplementary Figure S1. Additionally, 20 healthy age-, gender-, and ethnicity-matched controls were recruited. Of these, nine controls underwent CMR imaging. All participants provided informed consent prior to inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority (Ethical permit number: 2019-04253).

Table I. The demographic and disease-related characteristics of 34 newly diagnosed IIM patients at time of diagnosis.

Characteristics	
Age, years	67 (52-72)
Diagnosis delay, weeks	22 (12-37)
Gender, female, n (%)	18 (53)
Ethnicity, n (%)	
Caucasian	32 (94)
Asian	2 (6)
IIM subtype, n (%)	
IMNM	13 (38)
Anti-synthetase syndrome	10 (29)
Dermatomyositis	7 (21)
Overlap myositis	3 (9)
Polymyositis	1 (3)
Autoantibody profile, n (%)	
MSA	26 (76)
MAA	4 (12)
Seronegative	6 (18)
Clinical manifestation, n (%)	
Clinical myositis	25 (74)
Interstitial lung disease	18 (53)
Skin manifestation	12 (35)
Dysphagia	14 (41)
Arthritis	10 (29)
Disease activity measures	
Physician global disease activity VAS, 0-100	60 (47-60)
Patient global disease activity VAS, 0-100	80 (67-82)
Extra-muscular activity score VAS, 0-100	50 (20-60)
HAQ-DI, 0-3	0.56 (0-1.28)
Manual muscle testing, 0-80	75 (67-80)
CK, ukat/L [a]	16 (1.2-61.5)
Elevated CK (>3.5 ukat/L), n (%)	21 (62)
Treatments for IIM	
Prednisolone dose, mg	55 (17-60)
Patients on Prednisolone, n (%)	29 (85)
Methylprednisolone pulses, n (%)	4 (12)
Synthetic DMARD, n (%)	30 (88)
Rituximab, n (%)	6 (18)
Cyclophosphamide, n (%)	5 (15)
IVIG, n (%)	3 (9)

[a] normal reference range for CK is 0.6-3.5 ukat/L. Data are median (IQR) unless otherwise indicated. CK: creatine kinase; DMARD: disease-modifying anti-rheumatic drugs; HAQ-DI: Health Assessment Questionnaire-disability index; IIM: idiopathic inflammatory myopathies; IQR: interquartile range; mg: milligram; IMNM: immune-mediated necrotising myositis; IVIG; intravenous immunoglobulins; MSA: myositis specific antibody; MAA: myositis associated antibody; VAS: visual analogue scale.

Clinical and laboratory data collection

All study participants completed a comprehensive health questionnaire, they were evaluated by the same physician, and their medical histories were collected. Information regarding the presence of cardiac symptoms was gathered from patient interviews. Disease activity was assessed according to the Core Set Measures of the International Myositis Assessment & Clinical Studies Groups (IMACS) (22) using the physician's and patient's global assessment of disease activity, the standardised manual muscle test 8 (MMT-8), the Health Assessment Questionnaire Disability Index (HAQ-DI), serum level of muscle enzymes and extra muscular activity score (23). Presence of myositis was considered if at least two of the following were present at diagnosis: subacute proximal symmetric muscle weakness, elevated muscle enzymes (creatine kinase (CK), lactate dehydrogenase (LDH), myoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST)), pathological muscle biopsy or myopathic changes on electromyography. IIM patients were considered to have interstitial lung disease (ILD) if computed tomography described ILD changes, together with symptoms of dyspnoea and/or abnormal pulmonary function tests.

Assessment of myositis-specific and myositis-associated antibodies

All patient blood samples were analysed using the EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG) Profile (Euroimmun AG, Lübeck, Germany), which detects antibodies against Ro-52, OJ, EJ, PL-12, PL-7, SRP, Jo-1, PM-Scl-75, PM-Scl-100, Ku, SAE1, NXP2, MDA5, TIF1γ, Mi-2α, and Mi-2β. Testing was performed on the fully automated EUROBlotOne system (Euroimmun AG) at the accredited Laboratory of Clinical Immunology, Sahlgrenska University Hospital, following manufacturer's instructions. The band intensity was evaluated by the EUROLine-Scan program and intensity thresholds ≥15 were considered posi-

tive. Anti-HMGCR antibodies were measured in all myositis patients using the QUANTA Lite® HMGCR ELISA (Inova Diagnostics); values ≥20 Units were considered positive.

Cardiac investigations

- Cardiac injury/function markers as cTnI and N-terminal pro-brain natriuretic peptide (NT-proBNP)

An NT-proBNP value >125 ng/L was considered elevated, indicating the potential presence of heart failure according to European Society of Cardiology guidelines (24). Furthermore, a cTnI value >36 ng/L was considered as elevated according to the reference interval for cTnI at the Department of clinical chemistry at the Sahlgrenska University Hospital.

Electrocardiography (ECG)

A standard 12-lead ECG was performed and analysed according to current recommendations. Heart rate, cardiac axis, duration of the PQ-, QRS-, and frequency-corrected QT-interval (QTc), as well as presence of pathologic ST-T changes and arrhythmias (supraventricular *vs.* ventricular) were reported.

- Transthoracic echocardiography (TTE)

All TTE examinations were performed according to a standardised protocol using a commercially available imaging system (GE Healthcare, Milwaukee, Wisconsin, USA) equipped with a two-dimensional sector array transducer. Image analysis was performed in a blinded manner by an experienced imaging expert using EchoPAC (GE Healthcare, Milwaukee, Wisconsin, USA). Left ventricular dimensions (end diastolic volume (LV-EDV) and end systolic volume (LV-ESV) indexed to the body surface area (BSA)) and systolic function (EF) were assessed using the biplane Simpson method. Global longitudinal strain (GLS) was obtained using speckle tracking imaging from three apical standard projections. Cardiac output was determined using Doppler echocardiography (indexed to BSA). Valvular regurgitation was graded using the recommended multiparameter approach (25). Assessment of the tricuspid annular plane systolic excursion (TAPSE) by M-mode was performed at the lateral tricuspid annulus. The probability of the presence of pulmonary hypertension was assessed based upon the peak pulmonary artery pressure (PAP), with a threshold of >35 mmHg suggesting the presence of pulmonary hypertension (26).

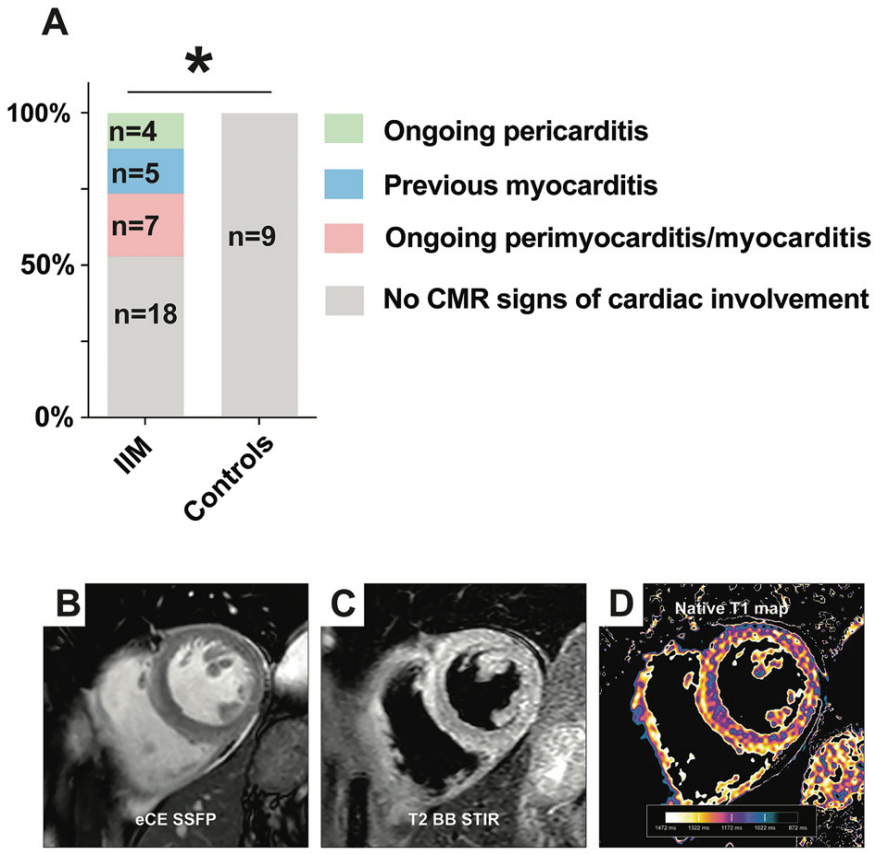

Fig. 1. A: Overview of CMR findings in 34 newly diagnosed IIM patients and 9 healthy controls. Representative CMR images from an IIM patient with ongoing myocarditis are shown. **B**: short-axis view demonstrating hyperaemia. **C**: myocardial oedema with a global T2 signal intensity ratio of 2.4. **D**: increased native T1-signal (1174 ± 53 ms *vs.* local reference 999 ± 31 ms). No signs of delayed enhancement were observed (not shown).
CMR: cardiac magnetic resonance; IIM: idiopathic inflammatory myopathies. *p<0.05.

- Cardiac magnetic resonance (CMR)

CMR imaging was performed using a 1.5 Tesla scanner (Ingenia, Philips Healthcare, Best, The Netherlands) with an anterior torso and posterior bed coil (dStream) according to a standardised protocol enabling the visualisation of cardiac inflammation in accordance with current recommendations (27). Image analysis was performed using CVI 42 (Circle Cardiovascular Imaging, Calgary, Canada) in a blinded manner by an experienced imaging expert and in accordance with current recommendations. Cardiac volumes and function of both ventricles were obtained by the slice summation method. The presence of cardiac involvement, both in form of a myocarditis and/or pericarditis was based on the Updated Lake Louise Criteria (15). Consequently, the presence of myocardial inflammation was based on the proposed "2 out of 2" approach, which means that one positive T2-based criterion (T2-weighted imaging or T2 mapping) and one T1-based criterion (T1 mapping, extracellular volume, or Late Gadolinium Enhancement, (LGE)) must be fulfilled. Previous myocarditis was identified by the presence of characteristic non-ischaemic LGE in the absence of signs of acute or ongoing myocardial inflammation. Due to practical issues, the interval between inclusion and CMR examination varied considerably, with a median of 12 days. Twenty-seven patients initiated prednisolone prior to CMR, and

12 patients initiated both prednisolone and disease-modifying anti-rheumatic drugs before CMR (3 cyclophosphamide, 7 methotrexate, 3 mycophenolate mofetil and 1 azathioprine).

Statistical analysis

Statistical analyses were performed using GraphPad Prism (v. 10.0.0). Descriptive statistics are presented as the median with interquartile range (IQR) or the number and/or the percentage, as appropriate. The difference between the patient group and control group was assessed by using Student's t-test (normal distribution) or Mann-Whitney U-test (non-normal distribution). The differences in frequencies were calculated by chi-square test. A correlation between cTnI and other variables was examined by the Spearman's correlation test and the coefficient expressed as Spearman's rho. For comparison among 3 subgroups, statistical analyses were performed using Kruskal-Wallis test with Dunn's post-test. A two tailed p-value <0.05 was considered statistically significant.

Table II. Differences among IIM patients with and without cardiac involvement and healthy controls.

	Healthy controls (n=9)	IIM without cardiac involvement (n=18)	IIM with cardiac involvement (n=16)
Age, years	57 (45-70)	67 (52-72)	66 (51-72)
Female, n (%)	5 (55)	10 (56)	8 (50)
BMI, kg/m^2	25 (22-27)	27 (22-32)	24 (21-27)*
Cardiac symptoms, n (%) [a]	0	5 (28)	4 (25)
IIM subtype, n (%)			
IMNM	-	6 (33)	7 (44)
Dermatomyositis		3 (17)	4 (25)
Anti-synthetase syndrome	-	8 (44.5)	2 (12)
Overlap myositis	-	0	3 (19)
Polymyositis	-	1 (5.5)	0 (0)
Autoantibody profile, n (%)			
MSA	-	14 (78)	12 (75)
MAA	-	1 (5.5)	3 (19)
Seronegative	-	4 (22)	2 (12.5)
IIM clinical manifestation, n (%)			
Clinical myositis	-	10 (55)	15 (94)*
Interstitial lung disease	-	11 (61)	7 (44)
Skin manifestation	-	7 (39)	5 (31)
Dysphagia	-	7 (39)	6 (38)
Arthritis	-	5 (28)	4 (25)

Values are presented as median (IQR), otherwise indicated. Student's t-test, Mann-Whitney U-test, and Fisher's exact test were used to compare IIM patients with and without cardiac involvement. Healthy controls used just as a reference.
BMI: body mass index; IIM: idiopathic inflammatory myopathies; IMNM: immune-mediated necrotising myositis; MSA: myositis specific antibody; MAA: myositis associated antibody.
*p<0.05. [a] cardiac symptoms such as chest pain, dyspnoea and/or palpitation.

Results

Patient characteristics

Out of the 40 patients, 34 underwent CMR and were included in the final analysis (Supplementary Fig. S1). The demographic and disease-related characteristics of patients is presented in Table I.

Median age was 67 years, and 53% were women. Muscle biopsy was performed in 82% of patients. The majority of patients were diagnosed either as IMNM (n=13, 38%) or ASyS (n= 10, 29%) while other subtypes occurred less often *i.e.* DM (n=7, 21%), overlap myositis (n=3, 9%) and PM (n=1, 3%). Among the 34 patients, 76% tested positive for myositis-specific antibodies (MSA) including anti-HMGCR, and 12% tested positive for myositis-associated antibodies (MAA) including anti-Ro52. The distribution of autoantibodies in patients with and without CMR-verified cardiac involvement is shown in Supplementary Table S1. High levels of anti-HMGCR antibodies were detected in 62% (n=8) of IMNM patients, all of them treated with statins. None of IMNM had positive SRP antibody. The most common anti-synthetase antibody was anti-Jo1 (n=7, 21%) followed by anti-PL7 (n=3, 9%). One patient with ASyS presented high reactivity for anti-EJ and another for anti-PL12. One patient exhibited simultaneous positivity for two anti-synthetase antibodies (anti-Jo1, anti-PL7). DM-related antibodies were detected in 7 of 34 (21%) patients as follows: anti-MDA5 (n=3), anti-SAE1 (n=1), anti-TIF1γ (n=1) and anti-Mi2 (n=1).

Regarding clinical manifestations, clinical muscle symptoms indicating myositis were present in 74% of the patients whereas 53% had ILD at time of IIM diagnosis. The occurrence of skin manifestation, dysphagia or arthritis was 35%, 41% and 29%, respectively (Table I).

CMR is superior to ECG/TTE in identifying IIM patients with heart involvement

Thirty-four IIM patients and 9 healthy controls underwent CMR, ECG and TTE investigations. The occurrence of CMR pathology was significantly more common in IIM patients compared to the healthy controls (p=0.016). None of the healthy controls showed detectable signs of cardiac involvement according to CMR. In contrast, 47% (n=16) of the 34 IIM patients demonstrated changes on CMR indicating cardiac involvement in form of ongoing myocarditis or perimyocarditis (n=7), ongoing pericarditis (n=4), or previous myocarditis (n=5). Notably, none of the patients with evidence of previous myocarditis had a clinical history of myocarditis, suggesting a subclinical cardiac involvement likely related to the underlying myositis (Fig. 1).

While there were no significant differences in TTE parameters between controls and IIM patients, ECG findings revealed that 35% of IIM patients displayed ST-T changes compared to none in controls (p=0.048) (Suppl. Table S2).

IIM patients with cardiac involvement exhibit myositis and more severe muscle damage

We further analysed the clinical, laboratory, ECG, TTE and CMR characteristics of IIM patients with CMR-

identified cardiac involvement (n=16) as compared to those without (n=18). Myositis as clinical manifestation was significantly more prevalent in IIM patient group with cardiac involvement (94%, p=0.018) compared to patients without cardiac involvement (Table II). Additionally, those patients had a lower median body mass index (BMI 24 *vs.* 27, p=0.043).

Laboratory analyses revealed significantly higher serum levels of myoglobin, AST, and ALT in the IIM patient group with cardiac involvement. While median CK levels did not differ between groups, a significantly greater proportion of patients with cardiac involvement had elevated CK levels (81% *vs.* 44%, p=0.027). Detailed results from laboratory tests, ECG, TTE and CMR findings are provided in Supplementary Table S3, Table S4, Table S5.

Elevated cTnI levels together with high muscle involvement markers indicate ongoing myocarditis/ perimyocarditis in IIM

Patients with ongoing CMR-verified myocarditis/perimyocarditis had significantly higher levels of myoglobin and cTnI compared to those with previous myocarditis. Additionally, 86% of patients with ongoing myocarditis/ perimyocarditis displayed elevated cTnI levels, which were significantly higher than in patients with ongoing pericarditis (p=0.015) and previous myocarditis (p=0.015) (Table III). In terms of ECG changes, patients with ongoing myocarditis/perimyocarditis demonstrated a significantly higher frequency of ST-T changes (71%) compared to those with previous myocarditis (p=0.027). No other significant differences were observed among the three groups regarding ECG or TTE results (Suppl. Table S6).

Correlation between cardiac injury markers and disease-related variables

We further explored the association between cTnI levels and various disease-related variables. A significant positive correlation was observed between cTnI levels and skeletal muscle activity markers (CK, LDH, myoglobin and AST), the presence of myositis, physician global assessment of disease activity, and prednisolone dose. Additionally, cTnI levels were positively correlated with ST-T changes on ECG, CMR findings of ongoing myocarditis/ perimyocarditis, and NT-proBNP levels. In contrast, a negative correlation was found between cTnI levels and the presence of MSA (Table IV).

Characteristics of IIM patients with severe cardiac involvement

To further evaluate the severity of cardiac involvement among patients with CMR changes (n=16), we stratified them based on cTnI levels. Three individuals had cTnI levels exceeding eight times the upper limit of the normal reference range (<36 ng/L). This cut-off was selected empirically based on the distribution of cTnI values in our cohort and corresponded to a natural threshold at which cTnI levels began to cluster among patients who also demonstrated clearly abnormal TTE parameters and/ or elevated NT-proBNP. All three patients were male, with a median age of 45 years, and they had significantly

Table III. Cardiac involvement in IIM patients includes ongoing myocarditis/perimyocarditis, ongoing pericarditis and previous myocarditis.

	Ongoing myocarditis/peri-myocarditis (n=7)	Ongoing pericarditis (n=4)	Previous myocarditis (n=5)
Age, years	63 (37-72)	69 (55-73)	68 (60-73)
Females, n (%)	3 (43)	3 (75)	2 (40)
CMR delay from treatment start, days	5 (2-12) [a*]	7 (6-32)	90 (21-105)
CK, µkat/L	44 (16-190)	52 (13-163)	1.6 (0.5-94)
Myoglobin, µg/L	1948 (353-5200) [a*]	3042 (349-4452)	45 (26-1150)
cTnI, ng/L	62 (29-970) [a* b**]	7.5 (5.7-10.5)	5 (5-5)
Elevated cTnI, n (%)	6 (86) [a* b*]	0	0
NT-proBNP, ng/L	865 (240-3630)	202 (86-273)	230 (91-301)
Elevated NT-proBNP, n (%)	6 (86)	2 (50)	3 (60)
ST-T changes on ECG, n (%)	5 (71) [a*]	0	0

Data are median (IQR; interquartile range), otherwise indicated.
IIM: idiopathic inflammatory myopathies; CK: creatine kinase; CMR: cardiac magnetic resonance; cTnI: cardiac troponin I; ECG: electrocardiography; NT-proBNP: N-terminal pro-brain natriuretic peptide. $^{*}p<0.05$; $^{**}p<0.01$.
[a] significant differences between IIM with ongoing myocarditis/perimyocarditis and IIM with previous myocarditis.
[b] significant differences between IIM with ongoing myocarditis/perimyocarditis and IIM with ongoing pericarditis.

Table IV. Correlation between cTnI levels and disease variables in 34 newly diagnosed IIM patients.

Variables	cTnI p-value (r)
Age, years	0.868 (-0.029)
Clinical myositis	0.011 (0.427)
Positive MSA	0.007 (-0.448)
PGA, VAS, 0-100	0.008 (0.443)
Prednisolone dose, mg	0.0003 (0.586)
CK, µkat/L	0.001 (0.515)
LDH, µkat/L	0.008 (0.457)
Myoglobin, µg/L	0.001 (0.532)
AST, µkat/L	0.001 (0.527)
CRP, mg/L	0.016 (0.408)
NT-proBNP, ng/L	0.0001 (0.618)
ST-T changes on ECG	0.001 (0.523)
Sign of ongoing myocarditis/perimyocarditis on CMR	<0.0001 (0.649)

AST: aspartate aminotransferase; CK: creatine kinase; CMR: cardiac magnetic resonance; CRP:C-reactive protein; cTnI: cardiac troponin I; IIM: idiopathic inflammatory myopathies; LDH: lactate dehydrogenase; MSA: myositis specific antibodies; NT-proBNP: N-terminal pro-brain natriuretic peptide; PGA: physician global assessment of disease activity; r: Spearman's Rho.

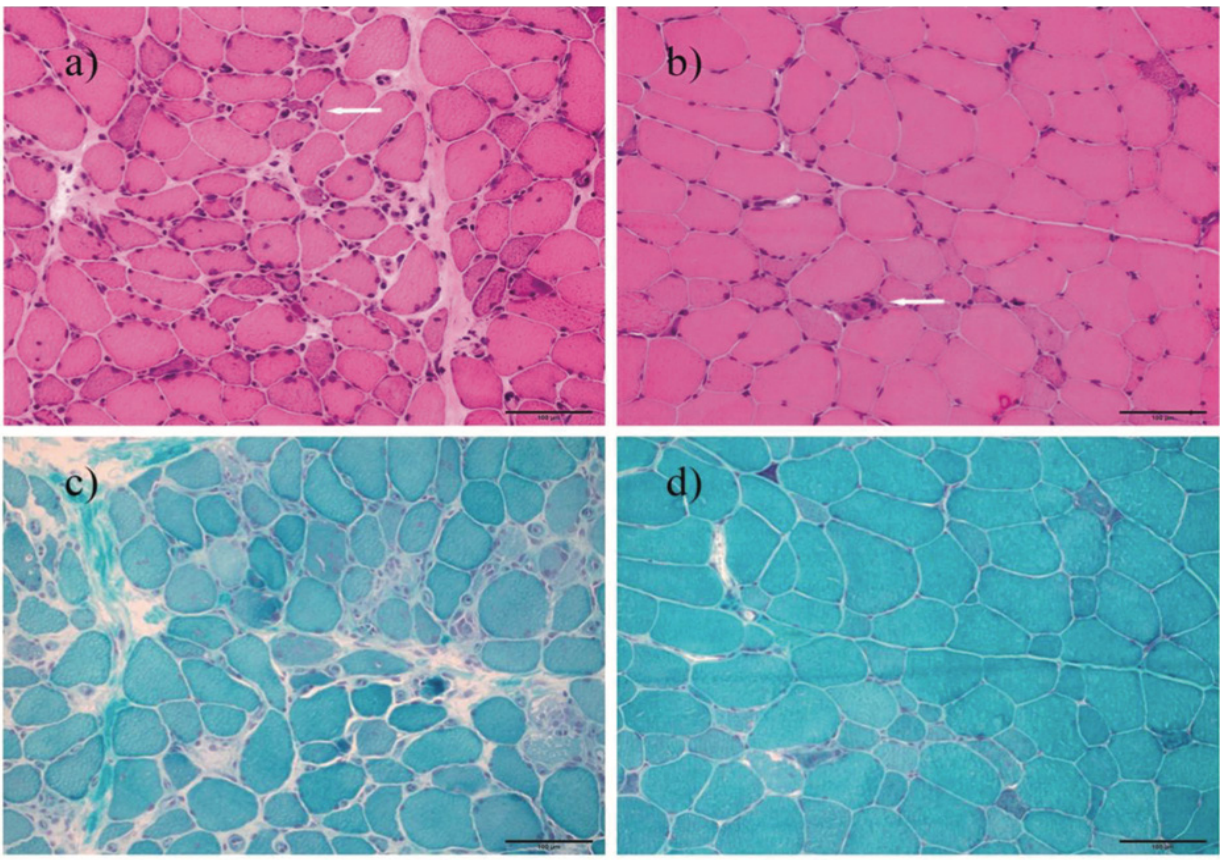

Fig. 2. Proposed diagnostic algorithm for early detection of cardiac involvement at the onset of idiopathic inflammatory myopathies.
CMR: cardiac magnetic resonance; ECG: electrocardiography; IIM: idiopathic inflammatory myositis; TTE: transthoracic echocardiography.

elevated levels of myoglobin and NT-proBNP (Suppl. Table S7). Moreover, these patients showed a significant impact on left ventricular function on TTE, with structural abnormalities on CMR being more severe. Collectively, these findings suggest that these patients may represent a subgroup with more severe cardiac involvement.

Discussion

Our findings demonstrate that cardiac involvement verified by CMR affects approximately 50% of patients with newly diagnosed IIM, with one-quarter of these cases presenting as pericarditis and the remainder as myocarditis or perimyocarditis. A key novel insight from this study is the close association between cardiac involvement and the extent of skeletal muscle involvement in IIM. Interestingly, IIM patients with cardiac involvement had lower BMI compared to those without cardiac involvement.

The current study suggests a potential association between cardiac involvement and skeletal muscle involvement, a relationship that has not been clearly demonstrated in previous studies. This association is supported by the observation that IIM patients with cardiac involvement more frequently exhibit skeletal muscle engagement and elevated skeletal muscle involvement markers. Moreover, elevated cTnI levels strongly correlated with markers of muscle activity, including CK, myoglobin, ALT, and AST. This finding aligns with our hypothesis that cardiac involvement may share a similar disease mechanism with skeletal muscle engagement. In a separate cohort, we demonstrated that the IMNM subtype is associated with clinical cardiac involvement in IIM patients (28). Notably, IMNM is known to present with more severe skeletal muscle involvement and higher levels of muscle damage markers (29). Consistently, autopsy studies have shown that histological signs of myocarditis in IIM patients include diffuse interstitial and perivascular mononuclear cell infiltration, resembling the inflammatory patterns observed in affected skeletal muscle (18). The observation that IIM patients with cardiac involvement have a lower BMI compared to those without cardiac involvement may be explained by more severe skeletal muscle involvement and associated muscle mass loss. Several factors such as type of autoantibodies could predict presence of cardiac involvement. Previous studies reported an association between the presence of anti-SRP and cardiac involvement (30, 31), and a link between antimitochondrial antibodies type M2 (AMA-M2) and a more severe cardiac involvement in IIM (32-34). In our cohort, however, the small sample size substantially limits statistical power, particularly within subgroups defined by CMR findings. These limitations may explain the absence of detectable associations with anti-SRP antibodies in our analyses. Moreover, AMA-M2 antibodies were not assessed in the present study, highlighting an important area for future investigation.

Cardiac involvement was a common

feature in patients with IIM in the current study, where approximately half of all IIM patients demonstrated CMR-verified cardiac involvement, which included findings such as pericarditis and myocarditis/perimyocarditis, while none of the healthy controls showed similar abnormalities. This aligns with a previous report in which cardiac abnormalities were detected in 67% of newly diagnosed IIM patients compared to 15% of healthy controls, using CMR and cardiac 99mTc-PYP scintigraphy (35).

In the present study, isolated pericarditis, in the absence of concomitant myocarditis, was identified by CMR but not by TTE in 4/34 patients with IIM. All 4 cases were clinically asymptomatic, a pattern consistent with observations in other autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis, where up to 50% of pericarditis cases were asymptomatic (36).

We identified three IIM cases with severe cardiac involvement by selecting a cut-off of eight times the upper reference limit for cTnI, a threshold that appears clinically reasonable. All three patients exceeding this level had markedly elevated NT-proBNP, and two of them also exhibited pathological ECG and TTE findings, including a significantly reduced ejection fraction. While this cut-off may be useful in identifying patients with severe cardiac involvement in clinical practice, it warrants validation in larger studies.

The long-term outcome and prognosis of cardiac involvement in IIM remain unclear. Regarding pericarditis, it is uncertain whether recurrent pericarditis occurs or if it could evolve into constrictive pericarditis. In contrast, myocarditis and perimyocarditis may be associated with severe clinical outcomes, despite the overall favourable prognosis. Most patients experience no long-term sequelae and have a low risk of recurrence (37). However, in severe cases, complications can arise (38). For instance, 45% of patients with biopsy-confirmed myocarditis developed major ventricular arrhythmias requiring an implantable cardioverter-defibrillator (39). In a large autopsy study of 10,199 young adults in Australia, myocarditis was identified as the cause of 12% of sudden deaths (40). Additionally, post-mortem studies for sudden cardiac death have reported myocarditis as the cause in up to 44% of fatal events in major series involving young individuals (41). It is well established that myocarditis can lead to fibrosis and subsequent heart failure, with up to 30% of biopsy-confirmed cases progressing to dilated cardiomyopathy (42). Data from the UK indicate that myocarditis patients requiring hospitalisation have an all-cause mortality rate of approximately 4%, with 20% of these deaths attributed to non-ischaemic dilated cardiomyopathy (43). In our cohort, only three patients (approximately 10% of all IIM cases) had severe myocarditis with markedly elevated cTnI and pathological findings. The remaining cases appeared mild, and the long-term prognosis of such myocardial involvement remains uncertain. Notably, patients with signs of previous myocarditis without active inflammation on CMR had received significantly longer prednisolone and other immunosuppressive treatments compared to those with ongoing myocarditis, suggesting a potential therapeutic effect of immunosuppressive treatments in IIM-related myocarditis. These findings also highlight the importance of performing CMR early, preferably before the initiation of glucocorticoids, to accurately assess cardiac involvement. Nevertheless, longitudinal follow-up studies are needed to further clarify the clinical course and long-term prognosis of cardiac involvement in IIM.

The current study has several limitations. First, the cohort size is relatively small, comprising only 34 IIM patients and 9 healthy controls. The number of patients with specific cardiac involvement subtypes is even smaller, only four patients had pericarditis and five had previous myocarditis, resulting in limited statistical power. However, a standardised CMR protocol for myocarditis was applied uniformly to all patients and controls, ensuring a robust and consistent definition of myocarditis. Second, due to practical constraints, not all IIM patients underwent CMR at the earliest stage after diagnosis. Consequently, some patients had received immunosuppressive treatment before imaging, potentially resulting in the resolution of mild pericarditis or myocarditis before it became detectable by CMR and/or might have altered the CMR findings and thereby the diagnosis based on the Updated Lake Louise Criteria.

Although our study has its limitations, our results are of utmost clinical relevance, which can be translated to the following algorithm for determining the presence of cardiac involvement in newly diagnosed IIM patients (Fig. 2). Since cTnI is a specific and sensitive marker for myocardial damage, all patients should undergo cTnI, ECG and TTE screening, particularly those with severe skeletal muscle involvement. Patients with normal cTnI levels may still have cardiac involvement, such as mild pericarditis. However, these patients are expected to respond favourably to immunosuppressive treatment, CMR may not be necessary for patients with normal cTnI levels. In patients with elevated cTnI levels, CMR should be considered to further evaluate potential cardiac involvement. While ECG and TTE might be useful baseline data for longitudinal follow-up, it seems to have limited usefulness to determine the presence of cardiac involvement in IIM at least close to IIM diagnosis. In cases where cTnI is elevated but CMR findings are unremarkable, additional clinical assessment should be considered to explore alternative explanations for the abnormal cTnI levels.

In conclusion, cardiac involvement is a frequent and often subclinical feature in newly diagnosed IIM with a strong association with the extent of skeletal muscle involvement, suggesting a shared pathogenic mechanism. While most cardiac manifestations were mild and clinically silent, a small subset exhibited severe myocarditis with potentially serious outcomes. Our findings highlight the clinical relevance of cardiac screening in IIM and support the use of cTnI as a sensitive biomarker for cardiac involvement. Further studies with larger cohorts and long-term follow-up are needed to validate these findings and better define the prognostic significance of cardiac involvement in IIM.

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