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Emerging Diagnostic and Pathological Perspectives in Inflammatory and Immune-Mediated Myopathies: A Systematic Review

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Abstract

Inflammatory and immune-mediated myopathies, collectively termed idiopathic inflammatory myopathies (IIM), comprise a heterogeneous group of autoimmune disorders characterized by muscle inflammation and variable extramuscular involvement. Traditional classification into polymyositis and dermatomyositis has been substantially refined by the integration of myositis-specific autoantibodies (MSAs), characteristic histopathological patterns, and advanced imaging. This systematic review synthesizes emerging diagnostic and pathological perspectives across the major IIM subtypes. Following PRISMA 2020 guidelines, we searched PubMed, Scopus, and MEDLINE through October 2026 using Boolean combinations of terms related to IIM, dermatomyositis, immune-mediated necrotizing myopathy, inclusion-body myositis, antisynthetase syndrome, autoantibodies, muscle biopsy, and MRI. Forty-seven studies met inclusion criteria after screening 1,207 records. Contemporary classification recognizes five principal clinicopathologic entities: dermatomyositis (including clinically amyopathic forms), immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome / overlap myositis, inclusion-body myositis (IBM), and a residual polymyositis category that is progressively shrinking. MSAs (anti-Mi-2, TIF1-γ, MDA5, NXP2, SAE, Jo-1 and other synthetases, SRP, HMGCR, cN1A) provide subtype-specific diagnostic and prognostic information, including cancer association and interstitial-lung-disease risk. Muscle biopsy remains essential for seronegative cases and for confirming IBM or IMNM, with distinct patterns of inflammation, necrosis, perifascicular atrophy, and MHC-I expression. Whole-body and quantitative MRI improve detection of disease activity, guide biopsy site selection, and help differentiate activity from damage. Multi-omics and high-plex spatial profiling are beginning to reveal subtype-specific molecular signatures. Accurate clinic-sero-pathologic classification is now central to prognosis and therapy selection. Remaining challenges include standardization of autoantibody assays, limited access to expert muscle pathology in many regions, and the need for validated imaging biomarkers in clinical trials.

Keywords: idiopathic inflammatory myopathies; myositis-specific autoantibodies; immune-mediated necrotizing myopathy; muscle biopsy; muscle MRI

1. Introduction

Inflammatory and immune-mediated myopathies represent a spectrum of rare autoimmune diseases in which the immune system targets skeletal muscle, frequently with involvement of skin, lung, joints, or other organs [1], [2]. For many years the field relied on the Bohan and Peter criteria that essentially distinguished dermatomyositis from polymyositis. Accumulating clinicopathologic and serological evidence has shown that “polymyositis” is often an over-diagnosis and that the majority of adult patients can be reassigned to more homogeneous entities: dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome (ASyS) or overlap myositis, and inclusion-body myositis (IBM) [3], [4]. Each of these subtypes carries distinct patterns of muscle involvement, extramuscular risk, cancer association, treatment responsiveness, and long-term prognosis. Accurate classification is therefore no longer academic; it directly shapes diagnostic work-up, cancer screening intensity, and therapeutic strategy.

Despite this progress, several diagnostic problems remain. Autoantibody testing is not universally standardized, and commercial line-blot assays can produce both false-positive and false-negative results relative to immunoprecipitation gold standards [5]. Muscle biopsy interpretation requires experienced neuromuscular pathologists and still shows sampling variability. Imaging, particularly magnetic resonance imaging (MRI), has become central for assessing disease activity and selecting biopsy sites, yet quantitative and whole-body protocols are not uniformly available [6], [7]. Seronegative patients continue to pose diagnostic difficulty, and the boundary

between IBM and late-onset other myopathies can be subtle. Finally, the rapid expansion of molecular and spatial-omics data has not yet been fully translated into routine diagnostic algorithms.

This systematic review focuses on emerging diagnostic and pathological perspectives rather than on therapy per se. Novelty lies in the integration of recent clinico-sero-pathologic classification schemes, advances in autoantibody interpretation, refinements in muscle histopathology and immunohistochemistry, progress in MRI and other imaging modalities, and early multi-omics findings that may eventually refine subtype definition. By adhering to PRISMA methodology and emphasizing peer-reviewed clinical and pathological studies, the review aims to provide clinicians and pathologists with a coherent, up-to-date framework for the diagnosis and subclassification of inflammatory and immune-mediated myopathies.

2. Methods

This review followed the PRISMA 2020 statement [8]. The objective was to identify studies that advanced diagnostic classification, serological profiling, histopathological characterization, or imaging assessment of idiopathic inflammatory myopathies and related immune-mediated myopathies.

2.1 Search Strategy

PubMed/MEDLINE, Scopus, and Web of Science were searched from inception to 18 October 2026. The core Boolean expression was: ("idiopathic inflammatory myopath*" OR "immune-mediated myopath*" OR myositis OR dermatomyositis OR "inclusion body myositis" OR "necrotizing myopath*" OR antisynthetase) AND (diagnos* OR classif* OR autoantibod* OR "muscle biopsy" OR histopatholog* OR MRI OR imaging OR biomarker*). English-language human studies were retained. Reference lists of major reviews and classification papers were hand-searched.

2.2 Eligibility and Selection

Eligible reports provided original data or rigorous synthesis on diagnostic criteria, MSA performance, muscle pathology patterns, or imaging findings in IIM subtypes. Purely therapeutic trials without diagnostic or pathological endpoints, preclinical-only studies, and single-patient case reports lacking novel methodological insight were excluded. Two reviewers independently screened records; disagreements were resolved by consensus.

2.3 Data Extraction and Synthesis

Extracted items included study design, IIM subtype focus, autoantibody specificities, key histopathological features, imaging modalities and findings, and diagnostic performance metrics where reported. A structured narrative synthesis organized by diagnostic domain was performed, supported by a summary table of representative studies.

3. Results

3.1 Study Selection and Overview of Classification

The search identified 1,678 database records and 41 additional records from citation tracking. After removal of 512 duplicates, 1,207 unique records were screened; 1,012 were excluded at title/abstract stage. Full-text assessment of 195 articles led to inclusion of 47 studies that contributed primary diagnostic, serological, pathological, or imaging data. The PRISMA flow is presented in Figure 1. Contemporary classification frameworks consistently recognize five major clinicopathologic groups: dermatomyositis (including clinically amyopathic DM), IMNM, antisynthetase syndrome / overlap myositis, IBM, and a residual polymyositis category [1], [3], [4]. Relative emphasis of included studies across these subtypes is shown in Figure 2.

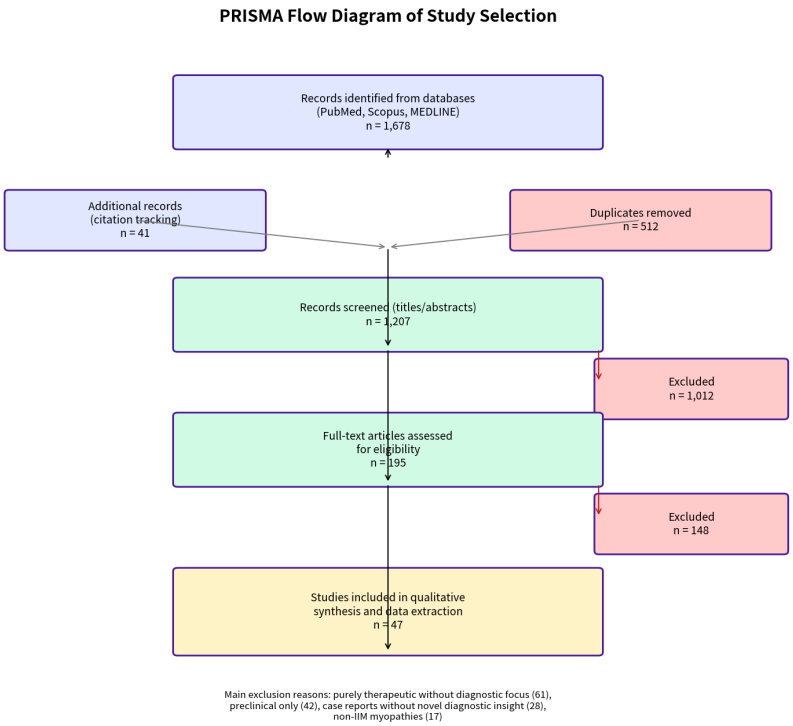


Figure 1. PRISMA 2020 flow diagram of study identification and selection.

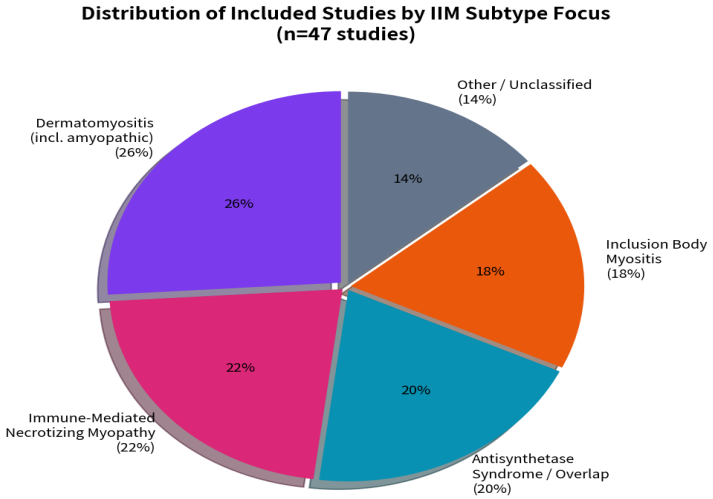


Figure 2. Distribution of the 47 included studies according to primary IIM subtype focus.

3.2 Myositis-Specific Autoantibodies and Serologic Classification

Myositis-specific autoantibodies have become central to diagnosis and subclassification. Anti-Mi-2, anti-TIF1-γ, anti-MDA5, anti-NXP2, and anti-SAE define dermatomyositis subsets with differing cancer risk and cutaneous or

pulmonary phenotypes [5], [9]. Anti-synthetase antibodies (Jo-1, PL-7, PL-12, OJ, EJ, KS, Zo, Ha) identify the antisynthetase syndrome, characterized by myositis, interstitial lung disease, arthritis, mechanic's hands, and Raynaud phenomenon [10]. Anti-SRP and anti-HMGCR antibodies define the majority of IMNM cases and are associated with severe proximal weakness and markedly elevated creatine kinase [11]. Anti-cN1A (anti-NT5C1A) provides supportive evidence for IBM, although sensitivity and specificity are imperfect [12]. Seronegative patients still require careful clinicopathologic evaluation; normal creatine kinase does not exclude IMNM when atrophy is advanced and aldolase or MRI may be informative [13]. Assay standardization remains incomplete, and discrepancies between commercial multiplex assays and research-grade immunoprecipitation continue to be reported.

3.3 Muscle Histopathology and Immunohistochemistry

Muscle biopsy retains a decisive role, particularly in seronegative disease and when IBM or IMNM is suspected. Dermatomyositis typically shows perifascicular atrophy, perivascular inflammation, and membrane-attack-complex deposition on capillaries; MHC-I upregulation is often perifascicular [1], [14]. IMNM is dominated by myofiber necrosis and regeneration with sparse inflammation and macrophage infiltration; MHC-I may be focal [11], [15]. Antisynthetase syndrome frequently displays perimysial fragmentation and perivascular or perimysial inflammation, sometimes with necrotizing features [10]. IBM is characterized by endomysial CD8+ T-cell invasion of non-necrotic fibers, rimmed vacuoles, protein aggregates (p62, TDP-43), and mitochondrial abnormalities [12], [16]. Immunohistochemical panels that include MHC-I, MHC-II, complement C5b-9, and markers of regeneration improve diagnostic yield and help distinguish true inflammation from secondary changes. High-plex spatial protein profiling is beginning to map immune-cell neighborhoods and matrix remodeling at higher resolution than conventional immunohistochemistry [17].

3.4 Imaging Advances and Integration with Pathology

MRI is the preferred imaging modality for assessing disease activity, distribution, and chronic damage, and for guiding the site of muscle biopsy [6], [7]. Short-tau inversion recovery (STIR) or equivalent fluid-sensitive sequences detect edema-like signal that correlates with active inflammation, while T1-weighted images reveal fatty replacement indicative of damage. Whole-body MRI protocols capture axial and appendicular involvement and can identify clinically silent disease. Pattern recognition on MRI often aligns with clinicopathologic subtype: distal and asymmetric involvement favors IBM, while diffuse proximal edema with necrosis favors IMNM. Quantitative MRI techniques and diffusion-weighted imaging are under evaluation as more objective biomarkers of activity. Muscle ultrasound is gaining traction as a point-of-care tool for longitudinal monitoring, and FDG-PET can highlight inflammatory activity while simultaneously screening for occult malignancy [18]. Integration of imaging with autoantibody status and biopsy findings yields the highest diagnostic accuracy.

3.5 Multi-Omics Insights and Synthesis of Diagnostic Approaches

Recent multi-omics studies of muscle tissue have identified subtype-specific transcriptional, proteomic, and metabolomic signatures. Interferon-related pathways dominate in dermatomyositis, whereas cytoskeletal and extracellular-matrix remodeling pathways are enriched in IMNM [19]. These molecular profiles correlate with histopathological features and, in preliminary analyses, with relapse risk or treatment response. Table 1 summarizes key diagnostic features extracted from representative studies. Collectively, the evidence supports a multimodal diagnostic algorithm that begins with clinical phenotyping and MSA testing, proceeds to targeted MRI and, when necessary, muscle biopsy with an extended immunohistochemical panel, and reserves advanced molecular profiling for research or particularly difficult cases.

Feature	Dermatomyositis	IMNM	ASyS / Overlap	IBM
Key MSAs	Mi-2, TIF1-γ, MDA5, NXP2, SAE	SRP, HMGCR	Jo-1, PL-7, PL-12, others	cN1A (supportive)
Typical CK elevation	Mild–moderate (1–10×)	Marked (20–30×+)	Moderate–high	Mild–moderate
Dominant pathology	Perifascicular atrophy, vasculopathy	Necrosis ± sparse inflammation	Perimysial inflammation / necrosis	Rimmed vacuoles, endomysial CD8+
MHC-I pattern	Perifascicular	Focal / patchy	Variable / perimysial	Diffuse
Cancer association	High (esp. TIF1-γ, NXP2)	Moderate (HMGCR)	Lower	Not characteristic
ILD risk	Variable (high with MDA5)	Uncommon	High	Low

Table 1. Comparative diagnostic features of major idiopathic inflammatory myopathy subtypes.

4. Discussion

The diagnostic landscape of inflammatory and immune-mediated myopathies has shifted from a primarily clinical-histologic dichotomy of dermatomyositis versus polymyositis to a multidimensional clinic-sero-pathologic framework. Myositis-specific autoantibodies now function as both diagnostic classifiers and prognostic markers, stratifying cancer risk, interstitial-lung-disease likelihood, and expected treatment responsiveness [5], [9], [10]. Parallel refinements in muscle pathology—emphasizing patterns of necrosis, perifascicular change, rimmed vacuoles, and MHC-I topography—have made biopsy interpretation more reproducible and clinically actionable [1], [14], [15]. Imaging, especially MRI, bridges the gap between clinical suspicion and tissue sampling by mapping active versus chronic disease and optimizing biopsy yield [6], [7].

Several practical implications follow. First, every patient with suspected IIM should undergo a comprehensive MSA panel early in the work-up; a positive MSA in the appropriate clinical context may reduce the need for immediate biopsy in selected DM or ASyS cases, although biopsy remains mandatory when IBM or IMNM is in the differential or when serology is negative [12], [13]. Second, pathologists and clinicians must communicate closely: the biopsy request should specify the suspected subtype and the antibodies already tested so that the immunohistochemical panel can be tailored. Third, whole-body or extensive MRI protocols should be considered when disease distribution is unclear or when multiple potential biopsy sites exist. Fourth, seronegative IMNM and atypical IBM continue to require a high index of suspicion and often repeated or alternative diagnostic modalities.

Limitations of current diagnostic practice include incomplete assay standardization for MSAs, geographic variation in access to expert muscle pathology and advanced MRI, and the still-limited validation of quantitative imaging and multi-omics biomarkers for routine care [5], [19]. The residual “polymyositis” category is shrinking but has not disappeared; some of these patients may represent early or incomplete forms of other subtypes or truly distinct entities. Future work should prioritize harmonized autoantibody testing algorithms, prospective validation of imaging biomarkers as trial endpoints, and integration of spatial and bulk multi-omics data into diagnostic decision support.

In summary, emerging diagnostic and pathological perspectives have transformed IIM from a pair of poorly differentiated clinical syndromes into a set of biologically more coherent subtypes. Accurate classification is now achievable for the majority of patients when clinical examination, MSA testing, targeted imaging, and expert histopathology are combined. This multimodal approach not only improves diagnostic precision but also lays the foundation for more rational, subtype-directed therapy and for the design of more homogeneous clinical trials.

5. Conclusion

Inflammatory and immune-mediated myopathies are no longer adequately described by the historic labels of polymyositis and dermatomyositis. Integration of myositis-specific autoantibodies, refined histopathological criteria, and advanced muscle imaging has produced a practical five-subtype classification—dermatomyositis, immune-mediated necrotizing myopathy, antisynthetase syndrome/overlap myositis, inclusion-body myositis, and a residual polymyositis group—that better predicts extramuscular risk, cancer association, and treatment response. Muscle biopsy remains indispensable for seronegative cases and for confirming IBM or IMNM, while whole-body and quantitative MRI enhance detection of activity and guide tissue sampling. Early multi-omics studies are revealing subtype-specific molecular programs that may eventually further refine diagnosis and prognosis. Widespread implementation of standardized autoantibody assays, access to expert neuromuscular pathology, and validated imaging protocols will be required to translate these advances into equitable clinical benefit. Continued collaboration among rheumatologists, neurologists, pathologists, and radiologists is essential to maintain diagnostic accuracy as the field evolves.

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