Clinical Correlation and Treatment Response of Anti-SAE Antibodies in Dermatomyositis: A Systematic Review

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Abstract

Dermatomyositis is an idiopathic chronic inflammatory disorder characterized by muscle weakness and distinctive cutaneous manifestations. It belongs to the spectrum of idiopathic inflammatory myopathies (IIMs), which includes polymyositis (PM), dermatomyositis (DM), and inclusion body myopathies. The detection of novel serotypes (specific myositis-specific antibodies) has sufficient sensitivity and specificity to facilitate a precise diagnosis and classification of DM. Some of the well-characterized MSAs in dermatomyositis include anti-Mi-2, anti-MDA5, anti-TIF1γ, anti-NXP2, and anti-SAE antibodies. Anti-small ubiquitin-like modifier activating enzyme (anti-SAE) antibodies have emerged as significant biomarkers associated with distinct clinical phenotypes in the study of DM. This study systematically reviews 22 articles, emphasizing clinical presentations, systemic associations such as interstitial lung disease (ILD) and malignancy, treatment response, and prognosis in anti-SAE-positive DM patients. Findings highlight the predominance of cutaneous manifestations, mild muscle involvement, and chronic ILD patterns. Anti-SAE-positive DM consistently displayed prominent cutaneous features, including heliotrope rash and Gottron's papules. Clinically amyopathic dermatomyositis (CADM) was observed in some cohorts. ILD occurred in 20–70% of cases, mainly presenting as chronic, mild to moderate patterns, with a higher prevalence in Asians than Western cohorts. Cancer rates varied widely, with European studies reporting a prevalence of 30% while Asian studies observed higher rates, reaching 57%. Immunosuppressive therapy, including corticosteroids and DMARDs, was effective in most patients, and hydroxychloroquine-induced skin flares were particularly notable in anti-SAE-positive cases. Anti-SAE-positive DM is a distinct subset with prominent skin manifestations, ILD risk, and regional differences in malignancy prevalence, necessitating tailored treatment strategies.

Keywords: *dermatomyositis, idiopathic inflammatory myopathies, clinically amyopathic dermatomyositis, myositis-specific antibodies, anti-SAE antibodies, interstitial lung disease*

1. Introduction

Idiopathic inflammatory myopathies (IIMs) represent a heterogeneous group of systemic autoimmune disorders that encompass polymyositis (PM), dermatomyositis (DM), and inclusion body myopathies. Clinically, these conditions are marked by proximal muscle weakness, muscle inflammation, extra-muscular manifestations, and often the presence of autoantibodies. Dermatomyositis (DM) is a rare idiopathic inflammatory myopathy characterized by a unique combination of proximal muscle weakness and distinctive cutaneous manifestations, such as heliotrope rash and Gottron's papules (Bohan, & Peter, 1975). The disease occurs across all age groups, with bimodal occurring peaks in childhood between the ages of 5 to 15 and adulthood in their late 40s to early 60s. The exact cause of dermatomyositis is not fully understood, but it is believed to be a complex interplay of the combination of genetic predisposition, environmental factors, and abnormal immune response. Pathophysiologically, DM involves immune-mediated microangiopathy, resulting in vascular injury mediated by complement deposition in the endomysial capillaries leading to muscle ischemia and necrosis (Lundberg et al., 2017).

Recent advances have identified myositis-specific autoantibodies (MSAs) that distinguish DM subtypes, each associated with peculiar clinical features and systemic complications, including interstitial lung disease, cardiac involvement, dysphagia, and malignancy (Tansley et al., 2013). For example, anti-

MDA5 antibodies are linked to a form of dermatomyositis that often lacks significant muscle involvement but is associated with rapidly progressive interstitial lung disease and a poor prognosis (Sato et al., 2005). Anti-TIF1γ antibodies are frequently associated with a higher risk of malignancy, particularly in adult patients (Ponyi et al., 2005).

Among these, anti-SAE antibodies, targeting a critical enzyme involved in SUMOylation processes, which is essential for cellular stress responses, were first described by Betteridge et al., (2007) have been linked to amyopathic and classic DM with severe skin involvement and dysphagia. These antibodies are realized as approximately 40-kDa and 90-kDa polypeptide bands, which are identified as SAE1 and SAE2. Anti-SAE antibodies were regarded as specific autoantibodies that can be found only in dermatomyositis patients, and there were also no case reports of these antibodies in other diseases apart from DM (Betteridge et al., 2009). Patients with anti-SAE antibodies may experience skin symptoms preceding muscle weakness, which is a distinguishing characteristic from other autoantibodies associated with DM. Patients often present with the classical cutaneous features of DM, including heliotrope rash and Gottron's papules, linked with a more severe cutaneous disease and a chronic course of skin involvement. However, some studies suggest that patients might have a relatively milder muscle disease compared to those with other autoantibodies, such as anti-Mi-2 or anti-Jo-1 antibodies (Tansley et al., 2013). Moreover, there is also an association between anti-SAE antibodies and the development of ILD and malignancies in some DM patients. According to previous studies, the prevalence of anti-SAE antibodies varies from 5% to 10% in the USA and Europe, compared to 2-3% in Asia. But the exact incidence and prevalence of anti-SAE antibodies are still unknown due to the lack of standardized and complete diagnostic criteria. Some preliminary surveys assumed that anti-SAE autoantibodies are found only in cases of adult DM and are not associated with juvenile DM. Now, some research has come out showing that anti-SAE antibodies are present at low prevalence in JDM. Anti-SAE positive DM remains a subject of significant research interest due to uncertainty in prevalence, associations with malignancies, and the challenges with its diagnosis and treatment response.

While numerous studies have focused on commonly detected MSAs, such as anti-MDA5 and anti-TIF1γ, limited data and variability in the reported findings exist regarding anti-SAE-positive DM in this relatively new era of study. This review seeks to synthesize the existing evidence on the clinical significance, systemic associations, and outcomes of the anti-SAE-positive dermatomyositis (DM) patient subgroup. By providing a comprehensive evidence base, it aims to support clinicians in making timely and accurate diagnoses, which are crucial for optimizing disease prognosis and improving patient outcomes. Additionally, this review contributes to the development of precise management strategies and guides future research directions.

2. Objectives

1) To investigate the updated, detailed information regarding the clinical correlation and characteristics of anti-SAE antibodies in dermatomyositis patients.

2) To assess the clinical relevance of anti-SAE antibodies in DM, including their diagnostic utility, association with systemic complications, and response to therapy.

3. Materials and Methods

This systematic review adheres to the PRISMA 2020 guidelines to ensure methodological rigor and transparency. A PICO (Population, Intervention, Comparison, and Outcomes) framework was employed to define the research question and guide the inclusion criteria. We thoroughly searched randomized controlled trials, prospective and retrospective studies, observational studies, and case series with more than five participants that assessed the prevalence, clinical significance, prognosis, or treatment response of anti-SAE antibodies in both adult and juvenile DM. Studies published between 2000 and 2024 in English were considered. Exclusion criteria included studies focusing on overlap syndromes where DM was not the primary diagnosis, case reports with fewer than five cases, and non-English publications. A comprehensive search was conducted using databases such as PubMed, Google Scholar, and the Cochrane Library. Search terms included a combination of MeSH terms and keywords such as "Dermatomyositis," "Idiopathic Inflammatory

Myopathies," "Small ubiquitin-like modifier activating enzyme", "Anti-SAE Antibodies," "Autoantibodies," "Clinical Features," "Prognosis," and "Prevalence." Boolean operators and truncations were applied to refine the search, supplemented by a manual reference screening of included studies and relevant reviews. For data collection, selection of studies was meticulously conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The journey of study selection from identification to final inclusion, highlighting the detailed steps involved, was shown in the following PRISMA flow diagram (Figure 1).

Two independent reviewers extracted data using a pre-designed form in Microsoft Excel, capturing study characteristics, participant demographics, diagnostic criteria, and clinical outcomes. Discrepancies were resolved through consensus or third-party consultation. Narrative synthesis was performed to summarize the study findings within the constraints of this systematic review. It is crucial for making sense of the vast amount of information collected and for drawing meaningful conclusions that can inform clinical practice, policy, or further research. The Newcastle-Ottawa Scale, as shown in Table 1, was used to evaluate the quality of the included studies and rated as poor, fair, moderate or good quality.

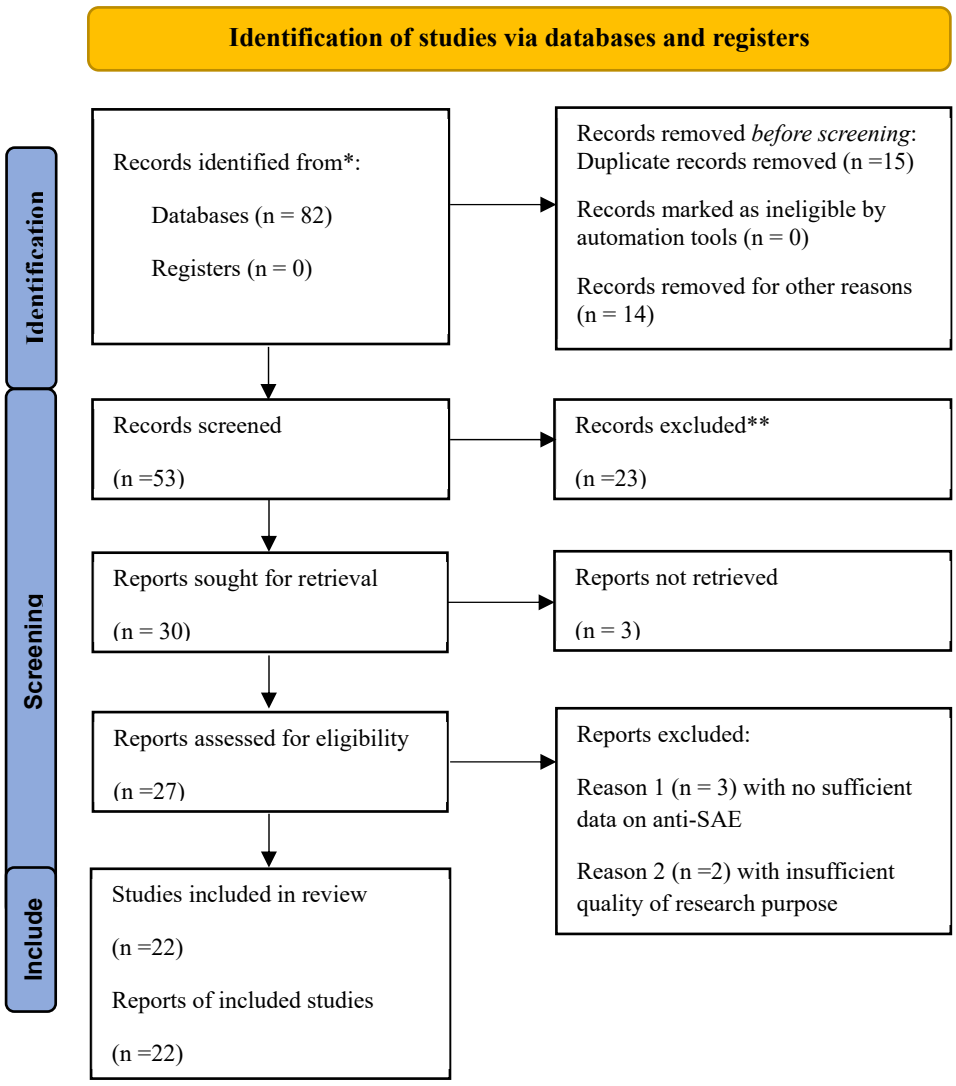

Figure 1 Workflow diagram describing a clear, visual summary of the study selection process [66]

Table 1 Quality assessment of included articles

Newcastle-Ottawa scale	Selection domain	Comparability domain	Outcome domain	Overall quality assessment
Betteridge et al., (2009)	3	1	1	5/9 Fair
Tarricone et al., (2012)	3	0	1	4/9 Fair
Muro et al., (2013)	3	0	1	4/9 Fair
Fujimoto et al., (2013)	3	0	1	4/9 Fair
Bodoki et al., (2014)	3	0	1	4/9 Fair
Muro et al. (2015)	4	0	1	5/9 Fair
Merlo et al., (2016)	3	0	2	5/9 Fair
Ge et al., (2017)	3	2	2	7/9 Good
Peterson et al., (2018)	3	1	2	6/9 Good
Inoue et al., (2018)	3	0	1	4/9 Fair
Wolstencroft et al., (2018)	3	0	2	5/9 Fair
Camins-Fàbregas et al., (2019)	3	0	2	5/9 Fair
Zuo et al., (2020)	4	2	2	8/9 Good
Albayda et al., (2021)	3	0	2	5/9 Fair
Tanboon et al., (2022)	4	2	1	7/9 Good
Babu et al., (2023)	2	0	1	3/9 Poor
Demortier et al., (2023)	3	1	2	6/9 Good
Depascale et al., (2023)	2	0	1	3/9 Poor
Fornaro et al., (2024)	4	1	2	7/9 Good
Xie et al., (2024)	3	1	2	6/9 Good
Zhang et al., (2024)	3	0	2	5/9 Fair
Hsiao et al., (2024)	3	1	2	6/9 Good

Maximum 4 stars for the selection domain
Maximum 2 stars for the comparability domain
Maximum 3 stars for the outcome domain

4. Results and Discussion

4.1 Results

Total twenty-two studies met our inclusion criteria after thorough and meticulous reviewing of full-text articles. Among the 22 articles reviewed, 14 specifically identified the presence of anti-SAE antibodies in patients diagnosed with dermatomyositis (DM). The remaining 8 articles also investigated the detection of anti-SAE antibodies within the broader context of idiopathic inflammatory myopathies (IIMs). Notably, the unique characteristics of anti-SAE antibodies were consistently associated with a definitive diagnosis of DM, with no evidence of overlap with other autoimmune diseases. Therefore, the remaining 8 articles also correlate with our inclusion criteria, as they contribute valuable insights into the detection and specificity of anti-SAE antibodies in DM.

Antibody detection methods are crucial for diagnosing and managing autoimmune conditions, such as dermatomyositis (DM), especially subgroups defined by specific and novel autoantibodies like anti-SAE. Immunoprecipitation (IP) is considered the gold standard for detecting anti-SAE antibodies due to its high sensitivity and specificity, allowing precise recognition of antibodies in their native conformations, but it is costly, prolonged, and often not accessible in the majority of laboratories (Hsiao et al., 2024). In addition,

line immunoassay (LIA) was also demonstrated to have a high concordance with IP results, having perfect sensitivity (100%), a high specificity of 99.6%, a positive predictive value (PPV) of 95.0%, and a negative predictive value (NPV) of 100% and indicating its excellent accuracy in detecting anti-SAE antibodies (Peterson et al., 2018). The combination of immunoprecipitation (IP) and line immunoassay (LIA) could enhance the detection of anti-SAE1 antibodies, thereby improving diagnostic accuracy and reliability. Enzyme-linked immunosorbent assays (ELISA) using recombinant SAE1 and SAE2 are effective for large-scale screening but may show variable specificity depending on antigen quality. The Western blotting method is used as a confirmatory anti-SAE positivity after initial screening with ELISA in Japanese DM patients following IP analysis for borderline cases (Fujimoto et al., 2013; Muro et al., 2013, 2015).

The prevalence of anti-SAE antibodies has been reported in 22 studies across diverse geographic regions, ranging from 0.29% to 12.6%, reflecting significant variability. This observation suggests that the occurrence of anti-SAE antibody positivity is notably lower in patients with autoimmune myositis compared to those with dermatomyositis. The highest prevalence of anti-SAE positive in DM patients was observed in the USA cohort (Wolstencroft et al., 2018), whereas the lowest was documented in the Japan cohort (Fujimoto et al., 2013). However, another cohort study (Xie et al., 2024) also exhibited similar lower prevalence of anti-SAE antibody positivity (1.6%) in dermatomyositis patients. The discrepancy in the prevalence of anti-SAE positivity across different countries may be attributed to differences in sample size, the utilization of diverse antibody detection methods, and variations in ethnic backgrounds. Asian trials, such as those from China (Zhang et al., 2024; Zuo et al., 2020) and Japan (Muro et al., 2015; Tanboon et al., 2022), consistently demonstrated intermediate prevalence levels, typically between 2% and 5%, which correlates with the literature review. Most studies reported a mean age of 55-60 years, indicating that anti-SAE is more prevalent among middle-aged to elderly individuals. A female predominance was noted in most surveys. The UK cohort demonstrated that anti-SAE antibody had a significant association with the HLA-DRB1*04-DQA1*03-DQB1803 haplotype ($p < 0.001$) (Betteridge et al., 2009).

Across all studies, anti-SAE-positive dermatomyositis (DM) was characterized by prominent skin involvement, including heliotrope rash, Gottron'papules, and photosensitivity. Approximately 90% of anti-SAE-positive DM patients were affected with classic skin rashes and had a higher chance of having skin itchiness ($P < 0.01$) (Fornaro et al., 2024). Unique features, diffuse erythematous rash such as the "angel wings rash" described in Japanese cohorts (Inoue et al., 2018), periungual changes, and the frequent occurrence of amyopathic DM (CADM) in some studies (Albayda et al., 2021; Fornaro et al., 2024; Hsiao et al., 2024; Merlo et al., 2017) highlight the cutaneous-dominant phenotype of this subset. Muscle involvement was generally mild, characterized by low-grade weakness or dysphagia, coherent across cohorts (Fujimoto et al., 2013; Muro et al., 2015). According to prominent findings from muscle biopsies in anti-SAE patients, such as perifascicular atrophy (53.3%), diffuse MHC-1 expression (60%), a less occurrence of degenerative muscle fiber necrosis, and unremarkable muscle damage, aligning with the less severe clinically muscle involvement observed in most patients (Demortier et al., 2023). The prevalence of dysphagia is ranging above 40% in anti-SAE positive DM patients, and feeding gastrostomy may be needed in severe cases (Betteridge et al., 2009; Ge et al., 2017). The disease initially manifests as skin rashes in the majority of cases (Bodoki et al., 2014) and developed prominent muscle involvement within 1 to 12 months. The median time from the onset of skin rashes to muscle involvement is approximately 4 months (3–7 months) (Zhang et al., 2024). An Italian cohort suggests that anti-SAE positive DM patients have a potentially less severe clinical course compared to other forms of DM that can present with systemic involvement (Tarricone et al., 2012).

Interstitial Lung Disease (ILD): ILD prevalence ranging from 20% to 70%, with chronic, mild to moderate patterns dominating. The presence of organizing pneumonia (OP) and nonspecific interstitial pneumonia (NSIP) was common (Zhang et al., 2024; Zuo et al., 2020). Although rapidly progressive ILD, though rare, was observed in some studies (Camins-Fàbregas et al., 2019; Fornaro et al., 2024), emphasizing the need for early diagnosis and management. In Asian anti-SAE-positive dermatomyositis (DM) analyses, the prevalence of interstitial lung disease (ILD) is notably higher, with reported rates of 71% in a Japanese cohort (Fujimoto et al., 2013) and 64% in a Chinese cohort (Ge et al., 2017). In contrast, European investigations have reported a lower prevalence of 18% (Betteridge et al., 2009). This evidence indicates that

anti-SAE antibody-positive DM patients exhibit clinical heterogeneity across different studies. Cancer prevalence varied significantly, with Asian cohorts reporting higher rates e.g., 57% in (Muro et al., 2015) compared to European studies e.g., 6.3% (Peterson et al., 2018). Frequently associated malignancies included colon, ovarian, and renal cancers. Studies such as (Merlo et al., 2017) and (Camins-Fàbregas et al., 2019) reported no malignancies, highlighting potential geographical or cohort-specific differences. Early diagnosis and prompt initiation of treatment are critical in managing ILD and its systemic symptoms effectively.

Most patients responded favorably to glucocorticoids and steroid-sparing agents; DMARDs are required in severe persistent skin disease conditions (Depascale et al., 2023). The disease-modifying antirheumatic drugs (DMARDs) administered included methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide, azathioprine, and other immunosuppressive treatments, along with hydroxychloroquine. The treatment regimen was observed as the initiation of medical therapies with glucocorticoids (prednisolone or methylprednisolone) alone or a combination of glucocorticoids and DMARDs after getting a diagnosis of DM positive with anti-SAE antibodies all over the studies. In long-term follow-up cases (median 21 months), nearly 80% of anti-SAE-positive DM patients responded positively to glucocorticoids and/or immunosuppressive agents, showing improvements in creatine kinase enzyme (CK) levels, Manual Muscle Testing 8 (MMT-8) scores, Modified Myositis Disease Activity Assessment Tool (MYOACT) scores, and Physician's Global Activity (PGA) scores. The average glucocorticoid dosage for these patients decreased from 61 mg/day to 25 mg/day. Additionally, some patients achieved full recovery of muscle strength, normalization of CK levels, and restoration of normal skin appearance, with minimal extramuscular disease activity. Anti-SAE antibody levels were associated with myositis disease activity, and patients positive for anti-SAE antibodies showed a favorable response to immunosuppressive treatment and experienced better outcomes (Ge et al., 2017). Furthermore, another Chinese study (Zhang et al., 2024) showed that one-third of patients achieved drug-free remission, whereas two-thirds of patients still needed oral prednisolone therapy at approximately 5mg daily, and some patients required only a single type of DMARDs and were able to discontinue oral glucocorticoids during a prolonged follow-up period of more than 12 months. The CDASI total activity score and Myositis damage index (MDI) score decreased from 18.7±7.0 to 0.9 ± 2.0 and 4.3 ± 3.1 to 1.2 ± 1.7, respectively. Drug-free remission was defined as the absence of all glucocorticoid and DMARD therapies for at least 12 months while maintaining a symptom-free state, with no recurrence of skin rash, muscle weakness, dysphagia, or constitutional symptoms.

Hydroxychloroquine-induced flares were observed in anti-SAE-positive DM patients ($P = 0.003$), with a median Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) score of 3 (interquartile range [IQR], 1–7) and a median follow-up duration of 40 months (IQR, 14–68) later than hydroxychloroquine exposure. These findings highlight the necessity for cautious use of the drug in this patient population. Interestingly, the presence of anti-MDA-5 autoantibodies exhibited a significant negative correlation with hydroxychloroquine-associated skin eruptions ($P = 0.006$) (Wolstencroft et al., 2018). Early initiation of immunosuppressive therapy was associated with improved outcomes in patients with anti-SAE-positive DM-associated ILD (Inoue et al., 2018). Significant radiological improvement was discovered at the moment of six months after receiving oral corticosteroids and intravenous immunoglobulins (IV IG) in these patients (Zhang et al., 2024).

Prognosis was generally favorable for anti-SAE-positive patients, with long-term survival rates exceeding 80% in many cohorts (Zhang et al., 2024). However, outcomes were influenced by complications such as malignancy and ILD. Chronic ILD cases were associated with better outcomes, whereas rapidly progressive ILD and malignancy significantly worsened prognosis in affected patients (Albayda et al., 2021; Babu et al., 2023; Demortier et al., 2023).

Table 2 Clinical characteristics of anti-SAE associated myositis

Author (Year)	Location	Anti-SAE Positive Patients	Prevalence (%)	Mean Age (Years)	Clinical Presentations	ILD Association (%)	Cancer Association (%)	Treatment Response	Prognosis
Betteridge et al., (2009)	UK	11/266	4.14	62	Typical DM skin rash; dysphagia common; mild ILD	18	18	Not reported	Generally good, mostly cutaneous DM
Tarricone et al., (2012)	Italy	5/130	3.85	NA	Skin and mild muscle symptoms	None observed	20	Not reported	Favorable
Bodoki et al., (2014)	Hungary	4/337	1.19	48	Classic DM; Gottron's sign, heliotrope rash and severe muscle weakness	None observed	25	Responsive to immunosuppressants	Generally good
Ge et al., (2017)	China	12/394	3	59	Hallmark cutaneous symptoms; dysphagia; mild muscle weakness	64	18	Effective glucocorticoid therapy	Generally good Antibody titers correlate with disease activity
Peterson et al., (2018)	USA	19/6445	0.29	55	Characteristic DM skin rash, Calcinosis, dysphagia, mild muscle weakness	57	Weak association (6.3)	Good response to corticosteroids and IVIG	Good; ILD & malignancy key factors
Albayda et al., (2021)	USA	19/2127	0.89	53	Severe cutaneous features, mild muscle involvement, CADM	55	26	Positive response to DMARDs	Good, except malignancy associated cases
Depascale et al., (2023)	France Italy	6/169	3.5	46	Characteristic DM skin rash, mild muscular weakness	50	16.7	Improved with MTX, MMF, IVIG and CYC	ILD and cancer risks
Hsiao et al., (2024)	Taiwan	70/6496	1.08	58	Skin rash, mild myositis, CADM	60	17	Good response to immunosuppressants	Generally favorable long-term survival

DMARDs, Disease-modifying antirheumatic drugs; MTX, methotrexate; MMF, mycophenolate mophetil; IVIG, Intravenous immunoglobulin; CYC, cyclophosphamide; CADM, clinically amyopathic DM; ILD, interstitial lung disease

Table 3 Clinical characteristics of anti-SAE positive dermatomyositis cases

Author (Year)	Location	Anti-SAE Positive Patients	Prevalence (%)	Mean Age (Years)	Clinical Presentations	ILD Association	Cancer Association	Treatment Response	Prognosis
Muro et al., (2013)	Japan	2/110	1.8	57, 70	Classic DM with mild muscle weakness	Mild ILD (PAH noted)	1Rectal cancer	Not reported	Not reported
Fujimoto et al., (2013)	Japan	7/456	1.5	67	Cutaneous rash, dysphagia, systemic symptoms	ILD in 71%	1 colon cancer (14%)	Not reported	Mild ILD and well response to therapy
Muro et al., (2015)	Japan	7/150	4.7	65	Cutaneous rash, dysphagia, systemic symptoms	Moderate ILD 57%	High rate (57%)	Not reported	High cancer risks influence outcomes
Merlo et al., (2016)	Italy	1/19	5.3	NA	Severe skin involvement, mild myositis, ADM	No ILD	No malignancies	Not reported	Not reported
Inoue et al., (2018)	Japan	7	NA	65	DM with diffuse erythema ("angel wings sign")	57%	28.5%	Good response to steroids and immunosuppressants	Early aggressive treatment may improve outcomes
Wolstencroft et al., (2018)	USA	14/111	12.6	49	Widespread skin disease, mild muscle symptoms	Not reported	Not reported	Hydroxychloroquine flares noted	Not reported
Camins-Fàbregas et al., (2019)	Spain	5/46	10.8	NA	Characteristic cutaneous involvement, dysphagia	40%	No malignancies	Responsive high dose corticotherapy, DMARDS, IVIG	High mortality due to respiratory diseases
Zuo et al., (2020)	China	6/165	3.6	52.7	Prominent cutaneous rash; mild systemic features	Organizing Pneumonia	Not reported	Not reported	Favorable with chronic ILD
Tanboon et al., (2022)	Japan	10/256	3.9	70.4	DM skin lesions, muscle weakness, dysphagia	30%	40%	Not reported	Not reported
Babu et al., (2023)	India	2/30	7.0	47	Not reported	Not reported	Significant association	Not reported	Not reported
Demortier et al., (2023)	France	49	NA	53	Typical Skin rash, cutaneous or mucosal ulceration	21%	16.3%	Immunosuppressive therapy successful	Moderate due to malignancy
Fornaro et al., (2024)	Italy	10/92	10.9	60	Classic DM and amyopathic DM, dysphagia	30%	20%	Require steroids and immunosuppressants	Favorable in long-term survival
Zhang et al., (2024)	China	47/1988	2.4	55	Multiple skin rash, mild muscle involvement	63.8%	15.4%	Positive response to DMARDs	High long-term survival rate
Xie et al., (2024)	China	4/293	1.6	52	Characteristic skin rash, myasthenia, dysphagia	25%	None reported	Not reported	Not reported

PAH, pulmonary arterial hypertension; NA, not applicable; ADM, amyopathic DM; Not reported, no data available

4.2 Discussion

The findings from this analysis place emphasis on the distinct clinical profile of anti-SAE-positive DM, characterized by typical cutaneous dominance and mild systemic involvement. Although anti-SAE-positive dermatomyositis (DM) patients exhibited classic DM features, secondary DM lesions such as cutaneous or mucosal ulcerations, cutaneous necrosis, and calcinosis were observed in certain cases. But these features were not statistically significant when compared to other MSAs in DM. Anti-SAE-positive DM patients had a significantly higher prevalence of skin itching ($p < 0.01$), shawl sign ($p < 0.05$), and lung involvement ($p < 0.05$) compared to anti-Mi2-positive patients. Additionally, they demonstrated lower creatine kinase levels ($p < 0.05$) and a reduced proportion of muscle fiber degeneration and necrosis ($p < 0.05$) in muscle biopsy analyses. While the variability in prevalence may reflect differences in patient populations and diagnostic techniques, the consistent association with CADM underscores the unique phenotype of this subset. ILD is a critical concern in anti-SAE-positive patients, affecting over half of the studied cohorts. Chronic and mild ILD forms predominate, with OP and NSIP being the most common radiological patterns observed on HRCT. However, the rare occurrence of life-threatening, rapidly progressive ILD necessitates vigilant respiratory monitoring and early intervention. The incidence of ILD is higher in Asian DM patients compared to European cohorts; this result may support the presence of genetic similarities among Asian people. Clinicians should prioritize timely ILD screening and close monitoring using high-resolution (HRCT) in dermatomyositis (DM) patients with high SAE1 autoantibody positivity, especially in Asian populations. Malignancy, although less prevalent in European cohorts, remains a significant risk factor for mortality in Asian studies, suggesting potential geographical or genetic influences. Although, the malignancy incidence rate in anti-SAE-positive DM is lower than in anti-TIF1-γ-positive DM but aligns with that observed in anti-NXP2-positive DM. For this reason, dermatomyositis (DM), irrespective of the autoantibody subset, is a high-risk condition of malignancy that demands comprehensive multi-system neoplastic screening at the early stages of diagnosis. The development of neoplasms in dermatomyositis (DM) may be driven by genetic and molecular mechanisms. Mutations or dysregulated expression of neoplastic autoantigen genes can trigger cross-reactivity against their corresponding proteins, potentially contributing to the pathogenesis of paraneoplastic myositis.

Glucocorticoids and DMARDs remain the cornerstone of treatment, with early initiation demonstrating substantial benefits. Hydroxychloroquine-induced skin flares, as highlighted by Wolstencroft et al., (2018), emphasize the need for alternative therapies tailored to anti-SAE-positive patients. But anti-MDA-5 autoantibodies showed a remarkable negative association with hydroxychloroquine-induced skin eruptions, while no other autoantibodies displayed a notable positive or negative correlation with this reaction. These findings may indicate underlying differences in disease mechanisms among various autoantibody subtypes. Advances in immunomodulatory drugs may further improve treatment outcomes for these patients. Present treatment guidelines are primarily informed by case series and retrospective studies, underscoring the need for well-designed clinical trials comparing different immunosuppressive and biologic therapies to determine the most effective treatment strategies for this patient subgroup. The prognosis for anti-SAE-positive DM is generally favorable when ILD and malignancy are managed effectively. Chronic ILD typically responds well to treatment, while rapidly progressive forms and malignancy remain key prognostic determinants. Long-term survival rates are encouraging, particularly in cohorts with early and aggressive management of systemic complications. Incorporating patient-reported outcomes and quality-of-life measures into research will provide a more comprehensive understanding of disease burden and treatment effectiveness.

This analysis highlights the need for early diagnosis, regular monitoring for ILD and malignancy, and tailored treatment strategies to improve patient outcomes. The observed regional variability in systemic complications suggests that genetic, environmental, and healthcare access factors may influence disease presentation and progression. Further research should focus on elucidating the molecular mechanisms underlying anti-SAE antibodies, exploring regional variations in systemic associations, and evaluating novel diagnostic and therapeutic approaches. Prospective multicenter studies with larger sample size, controlling of confounding factors, and the use of standardized diagnostic tools are essential to enhance subgroup analysis

and deepen our understanding of this rare but clinically significant DM subcategory. Strengthening international research networks can help pool resources, harmonize methodologies, and accelerate discoveries of anti-SAE positive DM in the future.

5. Conclusion

Anti-SAE-positive dermatomyositis is a discrete clinical subgroup characterized by prominent cutaneous manifestations, mild muscle involvement, and frequent systemic complications, such as ILD and malignancy. While the prognosis is generally favorable with early detection and treatment, complications like rapidly progressive ILD and malignancy warrant close monitoring because of significant negative impact outcomes. Tailored therapeutic strategies and future research focusing on larger cohorts, the use of uniform clinimetric assessments for evaluating treatment response and prospective designs are essential to refine the understanding and management of this unique subset of DM. Further research is needed to clarify the clinical manifestations, prognostic significance, and treatment responses of anti-SAE antibody-positive dermatomyositis (DM) patients compared to those with other myositis-specific autoantibodies (MSAs). Identifying these distinctions may improve diagnostic accuracy and inform targeted treatment strategies

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