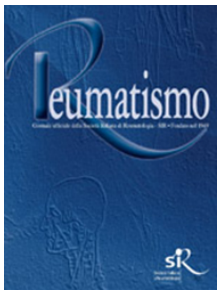

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Predictors of poor outcomes in juvenile dermatomyositis: what do we know? A narrative review

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Summary
Objective. Juvenile dermatomyositis (JDM) is a rare chronic systemic inflammatory disorder with a highly variable clinical course. It is important to identify the patients at risk of developing more severe disease. However, based on the existing literature, there is a lack of data regarding predictors of poor outcomes. Obtaining knowledge about clinical and laboratory risk factors for disease progression and severity at an earlier stage of the disease could potentially lead to a better long-term prognosis for patients with JDM.
Methods. A narrative review with the aim of identifying risk factors for poor outcomes in patients with JDM, such as death, severe disease, refractory disease, and functional impairment, was conducted. A total of 27 articles was included.
Results. Certain clinical manifestations and immunology features appear to worsen the prognosis in children with JDM. The recognition of these risk factors is essential for all pediatric rheumatologists as it allows the earlier identification of patients with potentially worse outcomes. These patients should receive closer follow-up and aggressive and individualized therapy in order to reduce their morbimortality.
Conclusions. Additional research is needed not only to identify more predictors of worse outcomes but also to identify more effective treatment approaches targeted toward these patients.

Introduction

Juvenile dermatomyositis (JDM) is a rare chronic systemic inflammatory disorder of childhood, with an incidence of 2-3 per million children per year (1, 2). Prior to the early 1960s, there were no effective treatments for children with JDM, resulting in poor outcomes, with approximately one-third incurring mortality and one-third serious disability (3). However, with the introduction of corticosteroids and other immunosuppressive agents, the mortality rate dropped to less than 2-3%, and a decrease in disease-related morbidity was observed as well (3). Nevertheless, some children have refractory disease and develop irreversible damage and disabilities that markedly impact their quality of life.

Because the clinical course of JDM is highly variable, it is important to identify the patients at risk of developing a more severe disease. However, based on the existing literature, there is a lack of data regarding predictors of poor outcomes. Obtaining knowledge about clinical and laboratory risk factors for disease progression and severity at an earlier stage of the disease could potentially lead to a better long-term prognosis for patients with JDM. Therefore, to help physicians identify patients at risk of developing severe disease, we aim to review the literature and identify different outcomes (such as mortality, severe disease, refractory disease, and functional impairment) and possible associated risk factors.

Methods

We searched PubMed using the terms “juvenile dermatomyositis” and “outcomes”, “prognostic factors”,” disease activity”, “mortality” or “functional impairment”, for articles published in English or Portuguese, from January 1, 2000, to December 31, 2022. From a total of 613 articles, 22 relevant articles about the predictors of different outcomes (mortality, severe disease, refractory disease, and functional impairment) were included. In addition, the reference lists of the included studies were manually searched for additional eligible studies, resulting in a total of 27 articles included in this narrative review.

Results

Predictors of mortality

A previous study that included 405 patients with juvenile idiopathic inflammatory myopathies (JIIM), comprising 329 with JDM, 30 with juvenile polymyositis, and 46 with juvenile connective tissue disease-associated myositis, aimed to identify risk factors for mortality in these patients. The authors found that the presence of antisynthetase antibodies (especially anti-PL-12 antibodies) and, to a lesser extent, the presence of anti-Ku antibodies seems to predict an increased risk of mortality (4). In terms of illness features, illness severity at onset, older age at diagnosis, overlap with other connective tissue diseases, and delay in diagnosis were associated with higher mortality (4). Dysphagia, dysphonia, abdominal perforation, interstitial lung disease, Raynaud’s phenomenon, and weight loss were the clinical features present prior to or at diagnosis that were recognized as mortality risk factors (4). To the best of our knowledge, this is the only study aimed at identifying predictors of mortality in patients with JDM. Table 1 describes the clinical features associated with poor outcomes in JDM patients.

Predictors of disease severity

Furthermore, certain factors have been identified as potential predictors of disease severity. An insidious onset and a chronic course (polycyclic or continuous), along with the presence of calcinosis or lipodystrophy, seem to be related to chronicity and higher disease activity (5, 6). In a retrospective study, Ravelli *et al*. evaluated 490 patients with JDM from inception cohorts seen between 1980 and 2004 in 27 centers in Europe (United Kingdom and Italy) and Latin America (Argentina, Brazil, and Mexico). They found that chronic course (polycyclic or continuous) appears to predict higher muscle weakness, as indicated by lower values on 8-muscle Manual Muscle Testing (7), and on Childhood Myositis Assessment Scale (CMAS) (8), as well as higher disease activity on both Myositis Disease Activity Assessment (MYOACT) (9) and Disease Activity Score (DAS) (5, 10). Furthermore, an

insidious disease onset predicted continued disease activity on both DAS and MYOACT. (5) Additionally, the presence of calcinosis or lipodystrophy was associated with a greater cumulative duration of active disease (5). A retrospective inception cohort of 59 patients diagnosed with JDM corroborated calcinosis as a predictor of higher disease activity based on MYOACT (6).
In a cohort of 84 patients with JDM, Stringer *et al*. found that the presence of rash, Gottron papules and nailfold abnormalities 6 months after the diagnosis were associated with a longer time to remission (11). Moreover, nailfold capillary abnormalities have been long recognized as a predictor of a chronic disease course and can be considered a noninvasive measure of disease activity (12-15). Numerous authors have identified an association between nailfold capillary abnormalities, particularly the loss of end-row nailfold capillaries, and the severity of muscle involvement (assessed by CMAS and muscle DAS) as well as skin involvement severity (evaluated through Skin DAS) (12-15). Additionally, the evidence of disease damage during the first year of diagnosis seems to predict ongoing active disease in long-term follow-up in a cohort of 59 patients with JDM (6).
Specific antibodies have also emerged as crucial indicators of disease severity. Notably, the presence of anti-transcription intermediary factor 1 (TIF-1)-γ, antisynthetase, anti-nuclear matrix protein 2 (NXP-2), anti-3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), anti-signal recognition particle (SRP), and anti-Ro-52 antibodies has been associated with an increased risk of severe, chronic, and refractory disease (16-20). In addition, patients with anti-melanoma differentiation-associated gene 5 (MDA-5) antibodies appear to require long-term treatment despite the presence of less severe changes in muscle biopsy (21). On the other hand, despite being associated with higher muscle weakness and dysphagia, anti-Mi-2 antibodies seem to confer a better prognosis due to a good response to conventional treatment (17). Table 2 presents the myositis-specific and myositis-associated antibodies and their implications for JDM prognosis.
Magnetic resonance imaging (MRI) findings at presentation seem to exert an influence on the subsequent clinical outcome (22). In a cohort of 45 patients with JDM who underwent a pelvic and thigh MRI, changes in the muscle or fascia were not found to be reliable predictors of clinical outcomes in children. However, the presence of abnormal subcutaneous fat signals appeared to be significantly associated with a more aggressive and chronic disease course (22).

Predictors of extramuscular involvement

Regarding extramuscular and extracutaneous involvement, specific autoantibodies seem to play a significant role. The presence of anti-MDA-5, anti-synthetase, and anti-Ro-52 antibodies has been associated with an increased risk of interstitial lung disease (ILD) (16, 18, 19, 23). Rider *et al*. found that anti-synthetase antibodies were associated with a higher risk of ILD compared to other antibodies studied (anti-Mi-2, anti-SRP, anti-NXP-2, and anti-TIF-1-γ) (18). A study involving 285 JDM patients, 21 of those positive for anti-MDA-5, showed that these antibodies were associated with ILD (23). Additionally, another study that included 302 patients with JDM, of whom 42 were positive for anti-Ro-52, found that these antibodies were strongly associated with ILD (19).
Furthermore, a reduced nailfold capillary density (NCD) has been linked to a higher risk of subclinical lung involvement (24). In a cohort of 58 patients with JDM, those with low NCD (<6 capillaries/mm) had lower forced vital capacity, total lung capacity and diffusing capacity for carbon monoxide values. Furthermore, signs of airway disease on high-resolution computed tomography were also more prevalent in the group with low NCD (24).
Anti-NXP-2 has been associated with gastrointestinal ulceration while anti-MDA-5 has been linked to skin ulceration (18, 23, 25). A study of a cohort of 285 JDM patients, which included 21 patients positive for anti-MDA-5, showed that these antibodies were associated with skin and oral ulceration (23).
In addition, vasculopathic features identified in the muscle and skin biopsies appear to be related to severe extramuscular manifestations, such as calcinosis, skin ulceration, ILD, and gastrointestinal tract involvement (26-28).

It is well known that calcinosis is one of the most severe complications of JDM. Several factors have been associated with an increased risk of calcinosis development (5, 29-31). A retrospective study involving 490 patients with JDM conducted by Ravelli *et al*. found an association between calcinosis and chronic, prolonged, and active disease (5). Longer disease duration, delay in diagnosis, and longer duration of elevated muscle enzymes were associated with calcinosis in a study conducted by Fisler *et al*. (31). Younger age at onset and anti-NXP-2 antibodies were associated with a higher risk of calcinosis in a cohort of 285 JDM patients aged less than 16 years (30). Additionally, prolonged disease duration, younger age at diagnosis, skin lesions (specifically Gottron papules), and periungual capillary changes were associated with calcinosis in a cohort of 49 patients with JIIM, 37 of them diagnosed with JDM (29). Lipodystrophy represents another severe complication and the presence of anti-TIF-1-γ antibodies seems to increase this risk (32). Moreover, in Ravelli *et al*.'s study Latin Americans had a higher susceptibility to developing both calcinosis and lipodystrophy in comparison to Europeans (5).

Predictors of functional impairment

In terms of functional outcomes, some factors have emerged as possible predictors of heightened functional impairment, including delayed diagnosis, inappropriate treatment, female gender, and chronic disease course (5, 31, 33). A retrospective study conducted by Bowyer *et al.* on 47 children with JDM found that patients treated late in the course of the disease and with low doses of corticosteroids were more likely to be functionally limited (33). Patients with chronic disease courses compared to those with monocyclic courses had more functional impairment (5, 34). Furthermore, female gender was identified as a predictor of functional impairment in two previous studies (5, 34).

Conclusions

In conclusion, certain clinical manifestations and immunological features appear to worsen the prognosis of children with JDM. Some of these include the presence of a chronic disease course, delayed diagnosis, occurrence of calcinosis and lipodystrophy, presence of antisynthetase antibodies, nailfold capillary abnormalities, and vasculopathic features identified in biopsies. Acknowledging these risk factors is essential for all pediatric rheumatologists, as it allows the prompt identification of patients at risk of poorer outcomes. Such patients should receive closer follow-up and tailored, aggressive therapeutic interventions in order to reduce their morbimortality. Thus, while anti-Mi-2 patients are likely to be best managed by standard conventional therapies, those with anti-NXP-2, anti-TIF-1-γ, anti-SRP, and anti-HMGCR may benefit from an alternative, more aggressive treatment approach. Patients with anti-MDA-5 and antisynthetase antibodies should be carefully monitored for the development of interstitial lung disease.

Further investigation is imperative, not only to identify additional predictors of worse outcomes but also to identify more targeted and efficacious treatment strategies tailored to these patients.

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Table 1. Clinical features associated with poor outcomes in juvenile dermatomyositis (JDM) patients.

Clinical features associated with poor outcomes in JDM	References
Higher mortality	
Illness severity at onset Older age at diagnosis Overlap with other connective tissue disease Delay in diagnosis Presence of dysphagia Presence of dysphonia Presence of abdominal perforation Presence of interstitial lung disease Presence of Raynaud phenomenon Presence of weight loss	(4)
Higher disease severity	
Insidious onset Chronic course (polycyclic or continuous) Presence of calcinosis Presence of lipodystrophy Presence of nailfold abnormalities Higher disease damage in the first year of diagnosis Presence of abnormal subcutaneous fat signal on MRI	(5, 6, 11-15)
Higher risk of extramuscular involvement	
Lung involvement Presence of reduced nailfold capillary density Presence of vasculopathic features in muscle and skin biopsies	(24, 26-28)
Skin ulceration and gastrointestinal tract involvement Presence of vasculopathic features in muscle and skin biopsies	(26-28)
Calcinosis Latin Americans Longer disease duration Chronic and active disease Delay in diagnosis Younger age at onset Presence of periungual capillary changes in capillaroscopy Presence of vasculopathic features in muscle and skin biopsies	(5, 28-31)
Lipodystrophy Latin Americans Longer disease duration Chronic and active disease	(5, 32)
Higher functional impairment	(5, 31, 33, 34)
Female gender Delay in diagnosis Inappropriate treatment Chronic disease course	

JDM, juvenile dermatomyositis; MRI, magnetic ressonance imaging.

Table 2. Myositis-specific and myositis-associated antibodies and their implications in juvenile dermatomyositis prognosis.

Antibodies	Implications	References
Anti-synthetase (anti-Jo-1, anti-PL-12, anti-PL-7, anti-OJ, among others)	Higher risk of ILD Increased risk of mortality	(17-19) (4)
Anti-TIF-1-γ	Increased risk of lipodystrophy Higher risk of skin ulceration Chronic disease with prominent skin involvement	(32) (32) (18)
Anti-Mi-2	Increased muscle weakness and dysphagia Better prognosis (good response to conventional treatment)	(17)
Anti-MDA-5	Rapidly progressive ILD Increased risk of skin ulceration Long-term treatment despite the presence of less severe changes in muscle biopsy Milder muscle involvement	(18, 23) (18, 23) (21) (17, 23)
Anti-NXP-2	Severe muscle involvement Increased risk of calcinosis Increased risk of gastrointestinal ulceration	(17, 18) (17, 18, 30) (16, 18)
Anti-HMGCR	Severe and refractory muscle disease	(17)
Anti-SRP	Severe and refractory muscle disease	(17, 18)
Anti-Ro-52	Severe, chronic, and refractory disease Increased risk of ILD	(19) (19)

ILD, interstitial lung disease; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; MDA-5, melanoma differentiation-associated gene 5; NXP-2, nuclear matrix protein 2; SRP, signal recognition particle; TIF-1-γ, transcription intermediary factor-1-γ.