Cutaneous ulcers in anti-MDA5-positive dermatomyositis with rapidly progressive interstitial lung disease: a multicentre retrospective cohort study

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Abstract

Introduction: To identify the clinical characteristics and risk factors for cutaneous ulcers in patients with anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis (anti-MDA5$^+$ DM) combined with rapidly progressive interstitial lung disease (RPILD).

Material and methods: We conducted a retrospective cohort study on the medical records of patients enrolled from the Nanjing Medical University Myositis-associated ILD cohort (NMMI). The clinical characteristics of patients in the ulcer-positive group were compared with those in the ulcer-negative group by chi-square or Fisher's exact test. Univariate and multivariate logistic regression analyses were used to assess risk factors for the development of cutaneous ulcers.

Results: A total of 246 patients with anti-MDA5$^+$ DM were retrospectively enrolled in the study, including 176 females (176/246, 71.54%) and 70 males (70/246, 28.46%), with a female-to-male ratio of 2.51 : 1. Among the 246 patients, a total of 88 cases (88/246, 35.77%) with anti-MDA5$^+$ DM combined with RPILD were further studied, including 55 females (55/88, 62.5%) and 33 males (33/88, 37.5%), with a female-to-male ratio of 1.67 : 1. Twelve patients (12/88, 13.64%) had cutaneous ulcers. In terms of clinical characteristics, patients in the ulcer-positive group had significantly more proximal muscle involvement (83.33% vs. 38.16%, $p = 0.003$) and more heliotrope rash (83.33% vs. 43.42%, $p = 0.010$) than in the ulcer-negative group. In univariate analysis, cutaneous ulcers were associated with proximal muscle involvement (OR = 8.103; 95% CI: 1.657–39.625; $p = 0.010$) and heliotrope rash (OR = 6.515; 95% CI: 1.336–31.773; $p = 0.020$). In multivariate analysis, cutaneous ulcers were associated with proximal muscle involvement (OR = 6.436; 95% CI: 1.274–32.524; $p = 0.024$), and proximal muscle involvement was an independent risk factor for cutaneous ulcers.

Conclusions: We confirmed the association between cutaneous ulcers and proximal muscle involvement and heliotrope rash in patients with anti-MDA5$^+$ DM combined with RPILD. Proximal muscle involvement is an independent risk factor for cutaneous ulcers.

Key words: dermatomyositis, anti-MDA5$^+$ dermatomyositis, rapidly progressive interstitial lung disease, proximal muscle involvement, heliotrope rash, risk factors.

Introduction

Dermatomyositis (DM) is a systemic autoimmune disease that affects the muscles and skin [1]. Anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis (anti-MDA5$^+$ DM) is an amyopathic subtype of DM that presents with the typical cutaneous manifestations of DM, such as Gottron papule, heliotrope rash, and shawl sign, combined with mucocutaneous ulcers [2]. This subtype of DM also is highly associated with rapidly progressive interstitial lung disease (RPILD) [2]. The cutaneous manifestations of DM and anti-MDA5$^+$ DM are heterogeneous and include maculae, heliotrope rash, nodules, and cutaneous ulcers [3]. Given the ease of skin examination, careful observation and familiarity with the clinical significance behind specific skin manifestations such as cutaneous ulcers may provide additional information to the clinician during physical examination. Nevertheless, the manifestation of various skin manifestations in DM and anti-MDA5$^+$ DM has not been adequately studied. Previous studies have shown a strong association between cutaneous ulcers and anti-MDA5 antibodies in the vast majority of anti-MDA5$^+$ DM patients, as well as an association with the presence of interstitial lung disease [4]. However, it is unclear whether cutaneous ulcers are of specific significance in the group of patients with anti-MDA5$^+$ DM with RPILD and whether the clinical features are the same in different groups of patients. This study aimed to assess the significance of the presence of cutaneous ulcers in patients with anti-MDA5$^+$ DM with RPILD.

Material and methods

We conducted a retrospective cohort study on the medical records of patients enrolled from the Nanjing Medical University Myositis-associated ILD cohort (NMMI). The NMMI is a multicentre, retrospective, longitudinal cohort with data from ten tertiary hospitals in East China. A total of 246 patients with anti-MDA5$^+$ DM were enrolled, of whom 88 patients with anti-MDA5$^+$ DM combined with RPILD were selected according to the study objectives, and their complete electronic data and medical record systems were used to collect general demographic, clinical characteristics, and laboratory data.

The inclusion criteria for this study consisted of patients older than 18 years of age who met the diagnostic criteria for anti-MDA5$^+$ DM, ILD, and RPILD [5–7]. ILD was diagnosed according to respiratory symptoms (dry cough and dyspnoea on exertion), physical examinations (such as Velcro rales in the lung bases), and high-resolution computed tomography (HRCT) findings (notable ILD findings such as ground-glass attenuations, consolidations, reticulations or honeycombing), with the exclusion of infection and drug-induced interstitial changes [7].

RPILD was defined as the acute and progressive worsening of dyspnoea onset within 3 months, with the presence of any of the following four conditions: (i) acute and progressive worsening of dyspnoea requiring hospitalization

or supplementary oxygen; (ii) lung function, including forced vital capacity (FVC), decreases by > 10%, or diffusion capacity for carbon monoxide of the lung falls over 15% with the decreased FVC; (iii) HRCT of the chest demonstrates that the extent of interstitial abnormalities has increased > 20%; (iv) arterial blood gas analysis suggests respiratory failure or the oxygen partial pressure reduction is > 10 mm Hg [8, 9].

The exclusion criteria for this study were patients with anti-MDA5$^+$ DM who were confirmed by two expert thoracic radiologists using HRCT not to have combined RPILD or who were under the age of 18 years.

The variables included in the study involved three aspects: general demographics (gender, age, duration of disease), clinical characteristics of anti-MDA5$^+$ DM (proximal muscle involvement (it denotes proximal muscle weakness), rash, Gottron papule, heliotrope rash, V sign, shawl sign, periungual erythema, arthritis, mechanic's hands, and cutaneous ulcers), and laboratory tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum ferritin, antinuclear antibody (ANA), anti-Ro52 antibody, and anti-amyl tRNA synthetase antibody (ARS)). Our definition of cutaneous ulcers includes any disruption of epidermal integrity (Figure 1) [4].

Regardless of the level of creatine phosphokinase, the assessment of proximal muscle involve-

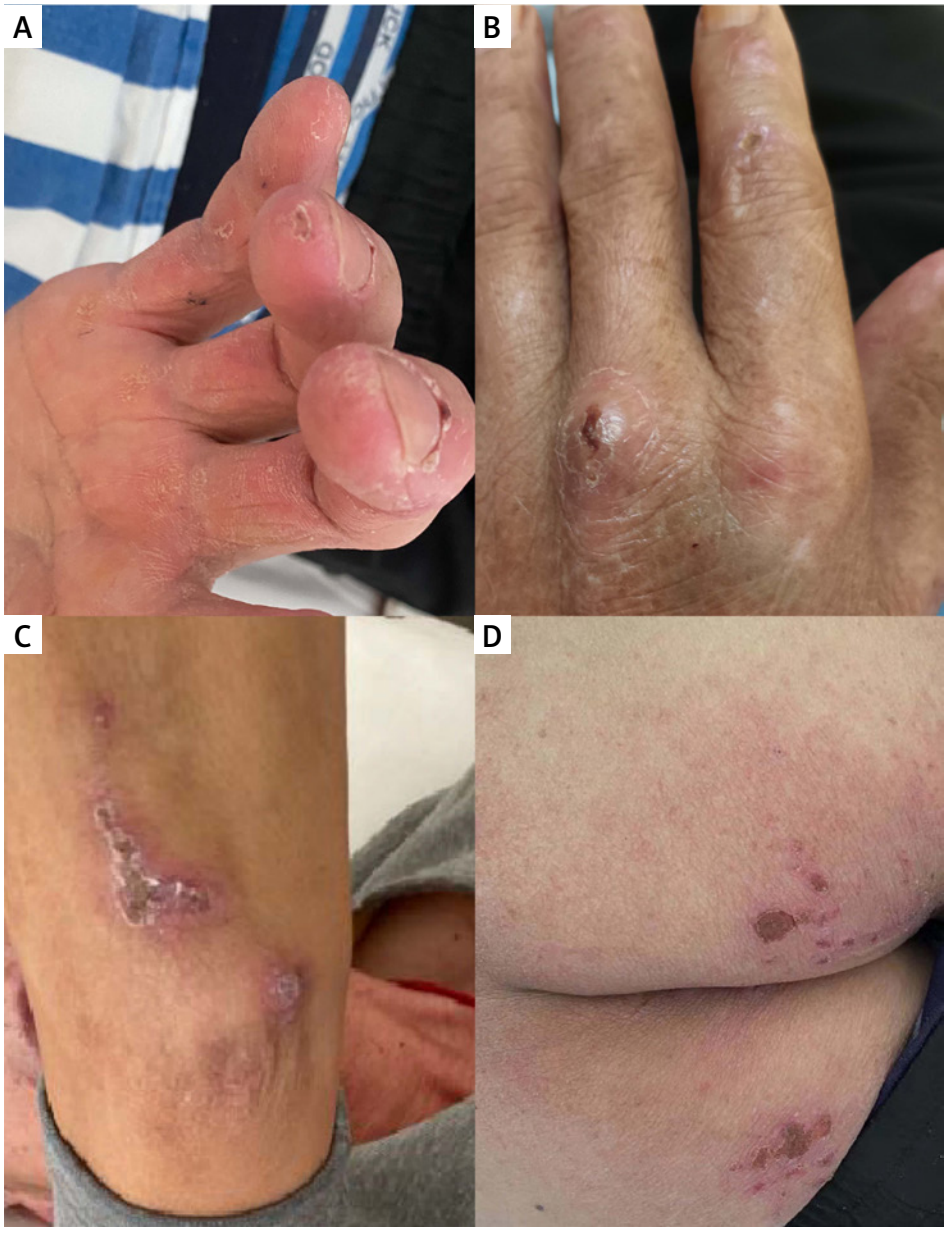

Figure 1. Location of cutaneous ulcers in anti-MDA5$^+$ DM patients: **A** – Ulcer on the fingertip. **B**, **C** – Joint ulceration. Ulcers over the Gottron papules and extensor surfaces. **D** – Ulcers in the buttock area

ment is the result of a comprehensive judgement: including: (i) detailed physical examination, especially assessment of proximal muscle strength; (ii) serum muscle enzymes (e.g., CK, LDH, ALT, AST, etc.), ESR, CRP, and antibodies to myositis (myositis-specific and myositis-associated antibodies); (iii) electromyography, muscle biopsy findings, muscle MRI of limbs (thighs and calves).

The Ethics Committee Board of the Second Affiliated Hospital of Soochow University approved the study protocol (ethical permit number No. JD-HG-2023-09). Due to the retrospective nature of the study and the anonymity of data, the requirement for informed consent was waived.

Table I. Baseline characteristics of a cohort of 246 patients with anti-MDA5⁺ DM enrolled from the Nanjing Medical University Myositis-associated ILD cohort

Variable	Total (n = 246)
Gender, *n* (%)	
Male	70 (28.46)
Female	176 (71.54)
Age, median (range) [years]	53.00 (47.00, 63.00)
Course of the disease, median (range) [months]	2.00 (1.00, 5.00)
Follow-up period, median (range) [months]	12.00 (3.00, 14.00)
Proximal muscle involvement#, *n* (%)	112 (45.53)
Rash, *n* (%)	229 (93.09)
Gottron papule, *n* (%)	168 (68.29)
Heliotrope rash, *n* (%)	140 (56.91)
V sign, *n* (%)	89 (36.18)
Shawl sign, *n* (%)	55 (22.36)
Periungual erythema, *n* (%)	52 (21.14)
Cutaneous ulcers, *n* (%)	34 (13.82)
Arthritis, *n* (%)	90 (36.59)
Mechanic's hands, *n* (%)	67 (27.23)
ALT, median (range) [U/l]	47.25 (29.00, 80.50)
AST, median (range) [U/l]	52.00 (32.88, 83.00)
LDH, median (range) [U/l]	333.00 (255.50, 426.50)
CK, median (range) [U/l]	63.00 (36.75, 158.00)
ESR, mean ± SD [mm/h]	41.99 ±23.85
CRP, median (range) [mg/l])	5.92 (3.10, 12.15)
Serum ferritin [ng/ml]	860.90 (343.73, 1500.00)
ANA positive, *n* (%)	129 (52.44)
Anti-Ro52 positive, *n* (%)	158 (64.23)
Anti-ARS positive, *n* (%)	15 (6.10)
Anti-MDA5 positive, *n* (%)	
(+)	72 (29.27)
(++)	46 (18.70)
(+++)	128 (52.03)
RPILD, *n* (%)	88 (35.77)
Death, *n* (%)	60 (24.39)

anti-MDA5⁺ DM – anti-melanoma differentiation-associated gene 5 positive dermatomyositis, RPILD – rapidly progressive interstitial lung disease, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CK – creatine kinase, LDH – lactate dehydrogenase, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, ANA – antinuclear antibody, anti-ARS – anti-aminoacyl tRNA synthetase. #Proximal muscle involvement denotes proximal muscle weakness.

Statistical analysis

The data collected in this study were statistically analysed using SPSS statistical software version 25.0 (IBM Corporation, Armonk, NY, USA). For categorical variables, frequencies and percentages were used to express the differences between groups compared by the χ^2 test or Fisher's exact test. For continuous variables, the Kolmogorov-Smirnov test and Levene χ^2 test were performed first, and the measures conforming to the normally distributed variables were expressed as mean ± S.D., and Student's *t*-test was used to compare the differences between groups, and measures with skewed distributed variables were expressed using median and interquartile range (P_{25}, P_{75}), and the Mann-Whitney *U*-test was used to compare the differences between groups. Risk factor analysis was first performed using binary logistic regression analysis, and then variables with $p < 0.05$ were included in multifactor logistic regression analysis to screen for independent risk factors for the development of cutaneous ulcers in patients with anti-MDA5⁺ DM combined with RPILD, and odds ratio (OR) values and 95% confidence intervals (95% CI) were calculated. Survival analysis was performed using the Kaplan-Meier method, and the log-rank test was used to compare the mortality rates between the two groups.

Results

Baseline characteristics of a cohort of 246 patients with anti-MDA5+ DM enrolled from the Nanjing Medical University Myositis-associated ILD cohort

A total of 246 patients with anti-MDA5⁺ DM were retrospectively enrolled in the study. Of these, 176 (176/246, 71.54%) were female and 70 (70/246, 28.46%) were male, with a female-to-male ratio of 2.51 : 1. The median age of all patients was 53.0 years, with a median disease duration of 2.0 months and a median follow-up of 12.0 months (Table I). The clinical features (including proximal muscle involvement, rash, Gottron papule, heliotrope rash, V sign, shawl sign, periungual erythema, cutaneous ulcers, arthritis, mechanic's hands, and RPILD) and laboratory indicators (including ALT, AST, LDH, CK, ESR, CRP, serum ferritin,

ANA, anti-Ro52 antibody, anti-ARS antibody, and anti-MDA5 antibody) were analysed. Among the 246 patients, 88 cases (88/246, 35.77%) of MDA5$^+$ DM with concomitant RPILD were further studied according to the research objectives.

Baseline characteristics of patients with anti-MDA5$^+$ DM combined with RPILD

According to the research objective, further analysis was conducted on 88 patients with combined anti-MDA5$^+$ DM and RPILD among 246 patients. Among them, 55 (55/88, 62.5%) were female and 33 (33/88, 37.5%) were male, with a female-to-male ratio of 1.67 : 1. The median age of all patients was 57.0 years, the median duration of disease was 2.0 months, and the median follow-up was 3.0 months. They were then divided into two groups for comparison based on cutaneous ulcers (Table II). In terms of demographic characteristics, there were no statistically significant differences between the two groups ($p > 0.05$). Importantly, in terms of clinical characteristics, patients in the ulcer-positive group had significantly more proximal muscle involvement (83.33% vs. 38.16%, $p = 0.003$) and more heliotrope rash (83.33% vs. 43.42%, $p = 0.010$) than in the ulcer-negative group. The remaining clinical features were not statistically significantly different between the two groups ($p > 0.05$). In terms of laboratory tests including ALT, AST, LDH, CK, ESR, CRP, serum ferritin, positive ANA, positive anti-Ro52

Table II. Baseline characteristics of 88 patients with anti-MDA5$^+$ DM combined with RPILD

Variable	Total (n = 88)	Ulcer positive (n = 12)	Ulcer negative (n = 76)	*P*-value
Gender, *n* (%)				0.354
Male	33 (37.50)	6 (50.00)	27 (35.53)	
Female	55 (62.50)	6 (50.00)	49 (64.47)	
Age, median (range) [years]	57.00 (49.25, 65.00)	56.75 ±10.75	58.50 (50.00, 65.00)	0.761
Course of the disease, median (range) [months]	2.00 (1.00, 3.00)	2.13 ±1.32	1.50 (1.00, 3.00)	0.489
Follow-up period, median (range) [months]	3.00 (2.00, 11.50)	3.00 (2.00, 10.25)	3.00 (2.00, 11.50)	0.592
Proximal muscle involvement#, *n* (%)	39 (44.32)	10 (83.33)	29 (38.16)	0.003*
Rash, *n* (%)	80 (90.91)	12 (100.00)	68 (89.47)	0.592
Gottron papule, *n* (%)	63 (71.60)	11 (91.67)	52 (68.42)	0.167
Heliotrope rash, *n* (%)	43 (48.86)	10 (83.33)	33 (43.42)	0.010*
V sign, *n* (%)	30 (34.10)	6 (50.00)	24 (31.58)	0.325
Shawl sign, *n* (%)	21 (23.86)	4 (33.33)	17 (22.37)	0.470
Periungual erythema, *n* (%)	20 (22.73)	4 (33.33)	16 (21.05)	0.457
Arthritis, *n* (%)	27 (30.68)	6 (50.00)	21 (27.63)	0.176
Mechanic's hands, *n* (%)	24 (27.27)	5 (41.67)	19 (25.00)	0.296
ALT, median (range) [U/l]	45.00 (29.80, 77.00)	35.25 (20.83, 85.00)	46.10 (30.00, 77.00)	0.379
AST, median (range) [U/l]	53.00 (39.00, 83.00)	55.40 (38.50, 132.75)	52.00 (39.00, 82.70)	0.369
LDH, median (range) [U/l]	380.00 (276.00, 547.00)	636.78 ±741.46	379.00 (276.00, 547.00)	0.584
CK, median (range) [U/l]	75.00 (33.50, 207.00)	137.50 (55.75, 559.35)	65.00 (33.00, 183.50)	0.072
ESR, mean ± SD [mm/h]	49.96 ±26.32	47.80 ±20.83	46.00 (30.10, 65.00)	0.926
CRP, median (range) [mg/l]	10.35 (3.98, 25.20)	9.50 (4.67, 27.00)	10.60 (3.87, 24.10)	0.990
Serum ferritin [ng/ml]	1369.30 (680.90, 2000.00)	1765.50 (471.15, 6016.20)	1268.95 (734.23, 2000.00)	0.293
ANA positive, *n* (%)	50 (56.8)	6 (50.00)	44 (57.90)	0.608
Anti-Ro52 positive, *n* (%)	77 (87.50)	10 (83.33)	67 (88.16)	0.642
Anti-ARS positive, *n* (%)	5 (5.68)	1 (8.33)	4 (5.26)	0.528
Death, *n* (%)	50 (56.82)	7 (58.33)	43 (56.58)	0.909

**Values statistically significant at p < 0.05. anti-MDA5$^+$. DM – anti-melanoma differentiation-associated gene 5 positive dermatomyositis, RPILD – rapidly progressive interstitial lung disease, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CK – creatine kinase, LDH – lactate dehydrogenase, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, ANA – antinuclear antibody, anti-ARS – anti-aminoacyl tRNA synthetase. #Proximal muscle involvement denotes proximal muscle weakness.*

Table III. Univariate and multivariate logistic regression analysis of the independent risk factors of cutaneous ulcers in patients with anti-MDA5⁺ DM combined with RPILD

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Proximal muscle involvement[#]	8.103 (1.657–39.625)	0.010*	6.436 (1.274–32.524)	0.024*
Heliotrope rash	6.515 (1.336–31.773)	0.020*	–	–

**Values statistically significant at p < 0.05. anti-MDA5⁺ DM – anti-melanoma differentiation-associated gene 5 positive dermatomyositis, RPILD – rapidly progressive interstitial lung disease, OR – odds ratio, 95% CI – 95% confidence interval. [#]Proximal muscle involvement denotes proximal muscle weakness.*

antibody, and positive anti-ARS antibody, there was no statistically significant difference between the two groups ($p > 0.05$).

Univariate and multivariate logistic regression analysis of the independent risk factors of cutaneous ulcers in patients with anti-MDA5⁺ DM combined with RPILD

In a univariate logistic regression analysis, cutaneous ulcers were associated with proximal muscle involvement (OR = 8.103; 95% CI: 1.657–39.625; $p = 0.010$) and heliotrope rash (OR = 6.515; 95% CI: 1.336–31.773; $p = 0.020$), but not with other demographic characteristics and clinical features. The differences were statistically significant for proximal muscle involvement and heliotrope rash as risk factors for cutaneous ulcers. In a multivariate logistic regression analysis, cutaneous ulcers were associated with proximal muscle involvement (OR = 6.436; 95% CI: 1.274–32.524; $p = 0.024$), and proximal muscle involvement was an independent risk factor for cutaneous ulcers (Table III).

Survival analysis between skin ulcer-positive and ulcer-negative groups in patients with anti-MDA5⁺ DM combined with RPILD

In our study, all participants were followed up for one year, with the endpoint event defined as the occurrence of death. Survival analysis revealed that there was no statistically significant difference in mortality between the skin ulcer-positive and ulcer-negative groups in patients with anti-MDA5⁺ DM combined with RPILD (log-rank $p = 0.849$) (Figure 2).

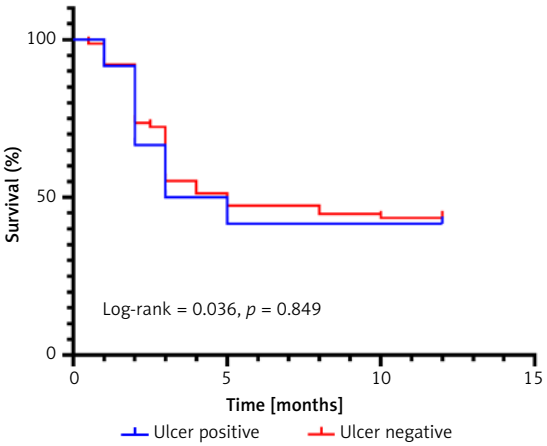

Figure 2. Survival analysis between skin ulcer-positive and ulcer-negative groups in patients with anti-MDA5⁺ DM combined with RPILD

Discussion

Anti-MDA5⁺ DM is a unique subtype of DM with distinct cutaneous and systemic manifestations, of which RPILD is its most dangerous systemic complication [2]. Other than typical cutaneous manifestations such as Gottron papule, heliotrope rash, V sign, shawl sign, and mechanic's hands, the most common cutaneous manifestation of anti-MDA5⁺ DM is cutaneous ulcers, with an estimated prevalence of 40–82% [10]. A previous cohort study including 152 patients with DM showed a strong association between cutaneous ulcers and anti-MDA5 antibodies in the vast majority of anti-MDA5⁺ DM patients, as well as an association with the presence of interstitial lung disease [4]. However, the clinical significance of cutaneous ulcers in patients with anti-MDA5⁺ DM combined with RPILD is not known. Our study confirmed the clinical features of cutaneous ulcers in patients with anti-MDA5⁺ DM combined with RPILD and found a strong association between cutaneous ulcers and proximal muscle involvement. Proximal muscle involvement is an independent risk factor for cutaneous ulcers. This suggests that patients with this skin manifestation should receive more detailed observation and clinical evaluation. Furthermore, cutaneous ulcers are highly symptomatic, painful, and easily visible to clinicians compared to ILD, which can provide significant diagnostic and additional information to clinicians and patients [4].

Cutaneous ulcers are one of the heterogeneous cutaneous manifestations of DM, which usually occur on the Gottron papules/signs, the digital pulp, or the periungual region, and can be extremely painful and poorly responsive to treatment [1, 10, 11]. Many factors can contribute to the development of cutaneous ulcers in patients with DM, such as vasculitis, vasculitis secondary to calcinosis, or scratching caused by pruritus and ischemia, with vasculitis considered to be the

main cause of cutaneous ulcers [12–14]. However, cutaneous ulcers in DM may also be the result of an underlying vascular lesion [4]. Studies have shown that skin biopsies from anti-MDA5$^+$ DM patients show underlying vasculopathy with endothelial cell ballooning and swelling, infiltration of mononuclear cells, and fibrin deposition in the vessel walls [13].

This study found a close association between cutaneous ulcers and proximal muscle involvement, and identified proximal muscle involvement as an independent risk factor for cutaneous ulcers. This finding has important clinical significance: First, in clinical diagnosis, patients with cutaneous ulcers, especially those with concurrent proximal muscle involvement in DM patients, are often encountered. By confirming the association between proximal muscle involvement and cutaneous ulcers, clinicians can be more vigilant of the risk of cutaneous ulcers in these patients and take early measures for intervention and treatment. Additionally, evaluating the proximal muscles of DM patients with existing cutaneous ulcers can provide important references for determining further treatment strategies and prognosis. Second, the results of this study are important for understanding the pathogenesis of cutaneous ulcers. Proximal muscle involvement may be closely related to inflammatory responses, immune dysfunction, and other factors that may be related to the occurrence and persistence of cutaneous ulcers. In-depth research into the relationship between proximal muscle involvement and cutaneous ulcers can provide a better understanding of these pathological processes and offer new directions for the development of future treatments and interventions. Third, the results of this study contribute to improving the prognosis and management of cutaneous ulcers. Considering that proximal muscle involvement is an independent risk factor for cutaneous ulcers, clinicians can pay more attention to this group and take early intervention measures to avoid further complications and deterioration. Furthermore, by assessing and monitoring the condition of proximal muscle involvement, doctors can better understand the disease progression and treatment effects of patients, providing a basis for developing individualized treatment plans. Finally, the results of this study provide new insights for further research and clinical practice. In future research, further exploration of the mechanisms related to proximal muscle involvement and cutaneous ulcers can provide a deeper understanding of their role in disease progression. Additionally, proximal muscle involvement can be explored as a biomarker for predicting the risk and prognosis of cutaneous ulcers, offering more accurate and reliable evidence for clinical decision-making.

Survival analysis of this study revealed that there was no statistically significant difference in mortality between the skin ulcer-positive and ulcer-negative groups in patients with anti-MDA5$^+$ DM combined with RPILD (log-rank p = 0.849). This finding may suggest that skin ulcers are not a major influence on anti-MDA5$^+$ DM mortality, but RPILD may be. The clinical significance of cutaneous ulcers in DM has been controversial in several previous studies. First, Nagashima *et al.* in their cohort found that the survival of DM patients with ILD and ulcerated Gottron sign was not worse than that of patients without ulceration [15]. Ulceration of the Gottron sign was not an adverse prognostic factor in patients with DM and ILD [15]. Second, the study by Cao *et al.* showed that DM patients with Gottron papule/sign with ulceration exhibited an increased risk of ILD and significantly lower cumulative survival rate [12]. The heterogeneity of the study population and the high frequency of positive anti-MDA5 antibodies in patients with Gottron papule/sign with ulceration in the cohort study by Cao *et al*. may explain the inconsistent results of the two aforementioned studies [9, 16]. A recent study showed that cutaneous ulcers did not correlate with RPILD and patient survival in the anti-MDA5$^+$ clinically amyopathic dermatomyositis with interstitial lung disease (CADM-ILD) cohort, which indicated that the combined presence of cutaneous ulcers and anti-MDA5 antibody did not further dampen the patient's prognosis [9]. In addition, it was found that not only the rate of anti-MDA5 antibody positivity was associated with the incidence of cutaneous ulcers, but also the level of this antibody titre was strongly correlated with the severity of cutaneous ulcers [12]. In view of these findings, we designed this study to explore the significance of cutaneous ulcers in the anti-MDA5$^+$ MD combined with the RPILD population to eliminate the interference of anti-MDA5 antibodies with the results. In conclusion, the value of cutaneous ulcers in DM remains to be further investigated in clinical practice.

Previous studies have highlighted the possible association of cutaneous ulcers with a high risk of malignancy [17–19]. However, the study by Cao *et al.* found no cancer in patients with ulcerative Gottron papules/Gottron sign, which may be related to the fact that two of the malignancy patients did not have skin biopsies at the location of the ulcer and the small sample size of the study [12]. Similarly, the study by Narang *et al.* did not reveal an association between cutaneous ulcers and internal malignancies [4]. After excluding the effect of MDA5 antibodies on tumours, still no significant association was found between skin ulcers and cancer (OR = 1.83, 95% CI: 0.60–5.58, p = 0.29) [4]. One explanation for this is that previous studies defined cutaneous necrosis (rather than

ulcers) as a clinical feature predictive of malignancy, a definition that may not correspond exactly with ulceration [4]. In our study, data on the tumour aspects of the patients were not included. Further future studies in the area of skin ulcers and tumours in patients with DM may additionally add to the clinical significance of cutaneous ulcers.

Previous studies have shown that abnormally elevated muscle enzymes are usually associated with severe proximal muscle involvement [20]. In our study, although there was a statistically significant difference in proximal muscle involvement between the two groups of patients, no statistically significant difference between the groups in levels of muscle enzymes including ALT, AST, and CK was observed. This may be related to the insufficient sample size in the ulcer-positive group. Further studies will be conducted in the future to confirm the association between muscle enzymes, proximal muscle involvement, and cutaneous ulcers. Notably, proximal muscle involvement is not only related to the disease of the muscle itself, such as DM, but also the duration of the disease. In general, the longer the duration of the disease is, the more severe is the muscle atrophy. In addition, in clinical practice, patients with cutaneous ulcers tend to use larger amounts of hormones. Therefore, the effect of proximal muscle involvement due to steroid myopathy on the results of this study cannot be ignored [21, 22]. In this study, proximal muscle involvement was obtained after the first physician's physical examination, and we could not re-evaluate it quantitatively. Considering the confounding factors mentioned above that interfered with this study, we will design further studies.

Our study has several limitations. First, our study had a retrospective design, so it cannot confirm a causal relationship between proximal muscle involvement and cutaneous ulcers, but it provides important preliminary data and clues. In the future, we need further prospective studies to validate our findings and better understand the relationship between proximal muscle involvement and cutaneous ulcers. Second, although our study found that only a few patients had cutaneous ulcers, our results may not be generalizable to other groups, especially patients from different countries or ethnic backgrounds. We also recognize that this phenomenon may be influenced by factors such as sample size limitations and study methodology, but that does not mean that this clinical presentation does not have clinical significance in reality. Third, there may be a certain diagnostic bias in the diagnosis of cutaneous ulcers in patients with anti-MDA5$^+$ DM combined with RPILD. Cutaneous ulcers may be influenced by various factors, including individual patient differences, clinical diversity, and inconsistent diagnostic criteria. Therefore, the number of patients with cutaneous ulcers found in our study may not fully reflect the true incidence of cutaneous ulcers in patients with anti-MDA5$^+$ DM combined with RPILD. Fourth, we did not investigate the impact of cutaneous ulcers in different parts of the body on the results of this study, such as joint extensor surfaces, digital pulp/fingernail lateral folds, shoulders, auricles, and soles of the feet. In addition, this study did not score the depth and size of cutaneous ulcers, nor did it stratify MDA5 antibody titres and muscle strength, which may lead to additional findings. Fifth, it is known that ferritin levels are related to the severity of anti-MDA5$^+$ DM and ILD [23]. However, in this study, there was no significant difference in ferritin levels between the ulcer-positive group and the ulcer-negative group. Ferritin levels are influenced by a variety of factors, including individual patient differences, inflammatory status, disease progression diversity, and the effects of therapeutic interventions. Therefore, our study results may not fully reflect the clinical significance of ferritin levels in the above different populations. Finally, it is known that the combined levels of carcinoembryonic antigen and ferritin reflect the severity of anti-MDA5$^+$ DM combined with ILD [24]. Given the basic design and limitations of our study, we were unable to provide data on carcinoembryonic antigen.

In conclusion, our study supports the significance of cutaneous ulcers in anti-MDA5$^+$ DM combined with RPILD, emphasizing the importance of observing this cutaneous clinical presentation in such populations.

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Ethical approval

The study methods were approved by the Ethics Committee Board of the Second Affiliat-

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Conflict of interest

The authors declare no conflict of interest.

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