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Clinical features and survival analysis of 40 cases of anti-MDA5 antibody-positive dermatomyositis complicated with interstitial lung disease

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Abstract

Background Several studies have shown that patients with anti-MDA5 antibody-positive dermatomyositis (anti-MDA5 antibody + DM) have an increased risk of developing rapid progression of interstitial lung disease (RPILD), which is associated with poor prognosis and high mortality. However, diagnosis and treatment are often delayed due to atypical early clinical features and heterogeneity. Therefore, clinical features should be identified to establish a prognosis model for early identification and intervention, thereby improving the clinical prognosis of patients.

Objectives The study aimed to investigate the clinical features, risk factors, treatment strategy, and construct a survival prognosis model for anti-MDA5 antibody + DM patients with ILD.

Methods A total of 40 anti-MDA5 antibody + DM-ILD patients admitted to the Department of Pulmonary and Critical Care Medicine and the Department of Rheumatology and Immunology in the Second Affiliated Hospital of Xi 'an Jiaotong University from September 2018 to May 2022 were retrospectively analyzed. Prognostic factors correlated with overall survival (OS) during hospitalization were identified by multivariate Cox regression analysis, and a nomogram was established. The nomogram was internally validated using C-index and time-dependent (at 1-, 2-, and 3-months) calibration curves with 1000 iterations of bootstrap resampling. Moreover, the optimal truncation values for continuous variables and Kaplan–Meier (K-M) curves were determined, which were used to analyze the difference in survival between groups. Finally, time-dependent decision curve analysis (DCA) was employed to validate the clinical value of the nomogram.

Results Significant differences were found between the survival group and the non-survival group in terms of age, oxygenation index, extent of lung lesions, diffuse alveolar damage (DAD) and nonspecific interstitial pneumonia (NSIP), and LDH, GLU, CEA, ferritin, CRP levels in serum ($P < 0.05$). Multivariate regression analysis revealed that increased NSIP in high-resolution computed tomography (HRCT) and ALT,LDH,CEA,CRP were risk factors for poor prognosis ($P < 0.05$). A nomogram diagram was constructed according to the final multiple Cox model to predict the 1-, 2-, and 3-month OS. According to ALT, AST, LDH, CEA, and CRP cutoff values, the KM algorithm was used

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to estimate the survival curve ($P < 0.05$). DCA curves were drawn for the model-dependent variables included treatment style, NSIP, ALT, AST, LDH, CEA, and CRP. This indicated that the nomogram yielded a higher net benefit compared to other single prognostic factors, and the cutoff value grouping model showed better practical application value. Combined treatment with glucocorticoids and immunosuppressants was a protective factor for long-term survival. Survival analysis indicated that patients with anti-MDA5 + DM-ILD could benefit from combined treatment for longer survival.

Conclusions Anti-MDA5 antibody + DM is prone to interstitial lung disease, poor prognosis, and high mortality. Risk prediction model could help us paying attention to these features which may allow the early identification of high-risk patients and promote timely diagnosis and treatment.

Keywords Anti-MDA5 antibody, Dermatomyositis, Interstitial lung disease, Prognostic factors

Introduction

Melanoma differentiation-associated gene 5 (MDA5) positive dermatomyositis (DM) is a rare subtype of idiopathic inflammatory myopathy, which was first reported in Japan. MDA5 is a cytoplasmic protein that plays a pivotal role in the host antiviral immune response, acting as a viral RNA sensor. Once activated, MDA5 can stimulate downstream signaling pathways to produce large amounts of type I interferon (IFN-I) and pro-inflammatory factors. Anti-MDA5 antibodies are a kind of myositis-specific antibody (MSA) first identified by Sato et al. in clinically amyopathic dermatomyositis (CADM) patients in 2005 [1]. A growing number of studies have shown that anti-MDA5 antibodies can be positive in DM, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA), etc. Nevertheless, it is still most commonly found in CADM (> 90%) and is strongly associated with progressing interstitial lung disease (RPILD) and poor clinical prognosis[2–5]. The treatment options include combined immunosuppressive therapy with glucocorticoids (GCs), cyclophosphamide (CY), and calcineurin inhibitors (CNIs), with the possible addition of rituximab (RTX) or plasma exchange (PE). However, many refractory cases have been reported. Anti-MDA5 antibody + DM may be classified into two subtypes depending on the onset and progression of the disease, namely acute/subacute interstitial pneumonia (A/SIP) and chronic interstitial pneumonia (CIP). The incidence of A/SIP is significantly higher than that of CIP, resulting in a considerable proportion of patients presenting with RPILD early in the disease [6–8], leading to a poor prognosis. Previous studies reported that the 6-month survival rate of anti-MDA5 antibody + DM-RPILD ranged between 40.8% to 45.0%[9]. Therefore, identifying early risk factors and clinical characteristics of anti-MDA5 antibody + DM-interstitial lung disease (ILD) patients and establishing a survival prognosis model may lay a foundation for subsequent survival prognosis studies.

This study aimed to investigate the clinical phenotype and characteristics, prognostic factors, and survival prediction indicators of anti-MDA5 antibody + DM-ILD patients, especially those suffering from RPILD, to improve the early diagnosis rate and treatment success rate, while improving the prognosis of this disease.

Material and methods

Study sample

Patients admitted to the Department of Pulmonary and Critical Care Medicine and the Department of Rheumatology and Immunology in the Second Affiliated Hospital of Xi 'an Jiaotong University from September 2018 to May 2022 were retrospectively analyzed. The inclusion criteria were as follows: (1) relatively complete case data; (2) positive serum anti-MDA5 antibodies; (3) conformed to the diagnostic criteria of ILD: ① dry cough, dyspnea after activity, and velcro rales with no obvious cause; ② pulmonary interstitial abnormalities were detected by high-resolution computed tomography (HRCT), including grid-like, patchy, honeycomb, and thread-like shadows. ③ pulmonary function tests showed restricted ventilation function or diffusion dysfunction; ④ confirmed by surgical lung biopsy. ILD could be diagnosed by the presence of two items from items ① ② ③, or by item ④ alone, excluding pulmonary tuberculosis and emphysema. RPILD was defined as an increase in lung symptoms, imaging findings, or rapid deterioration of lung function within 3 months. Patients were excluded from this study if they met any of the following criteria: (1) patients with incomplete case data; (2) patients under 18 years of age; (3) ILD caused by infection (including SARS-CoV-2 infection), drugs, or other diseases. A total of 46 cases were included in the study (Fig. 1).

Data collection

The baseline characteristics of patients diagnosed with anti-MDA5 antibody + DM-ILD were retrieved from the electronic medical record system of the Second Affiliated Hospital, Xi'an Jiaotong University. The general demographic information, including age, gender, smoking

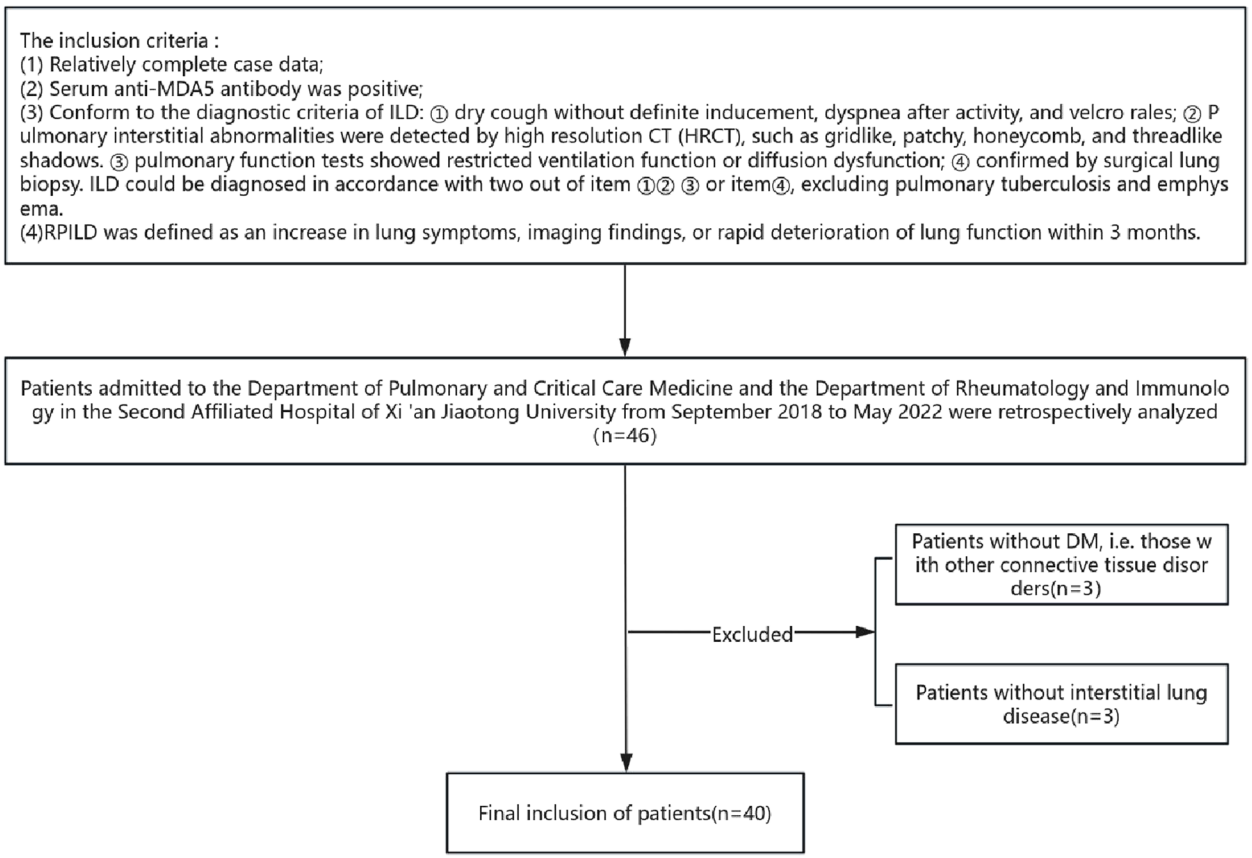

Fig. 1 Clinical study flow chart

status, diagnostic time, as well as clinical manifestations, laboratory and imaging examination, and treatment details were extracted from the medical records. Clinical manifestations mainly included fever, dry cough, dyspnea, joint and muscle symptoms (muscle soreness, muscle weakness, and joint pain), and skin vascular damage (periorbital redness, technician's hand, Gottron's sign, V sign, sun rash, cape sign, and skin ulceration). Laboratory examination mainly included routine blood tests, biochemical indexes, CRP, ESR, tumor-related biomarkers, autoantibodies, myositis antibody spectrum, etc. Among above index, anti-MDA5 antibody and anti-Ro-52 antibody was detected by immunoblotting, and presented in a semi-quantitative manner of - ~ + + +.

Image acquisition

Chest HRCT was performed using a second-generation dual-source CT machine (SOMATOM Definition Flash CT, Siemens Healthineers) with high-pitch spiral scan mode. Patients were positioned supine with both arms up. The scan range was from the top to the bottom of the lung in the cranio-caudal direction. The scanning parameters were as follows: the tube voltage ranged from 80 to 100 kV and an automatic tube current was used; the section thickness was set at 5 mm for conventional chest CT and 1 mm for HRCT; the lung window settings were configured with a window width of 1500 HU and a window level of −500 HU, while the mediastinal window had a window width ranging from 300 to 400 HU and a window level of 10 to 20 HU. The imaging findings related to ILD, including diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP), organized pneumonia (OP), usual interstitial pneumonia (UIP), and mediastinal emphysema, were assessed by a multidisciplinary team (MDT) consisting of more than two experienced radiologists and pulmonologists. Extent of lung lesions means the scale of shadow in the lung. Shadow area less than 25% is 1 point, more than 25% and less than 50% is 2 point, and more than 50% is 3 point. Patient follow-up was carried out via telephone consultations and outpatient visit.

Definitions

DM was defined based on the diagnostic criteria of inflammatory myopathy proposed by the European League Against Rheumatism and the American College

of Rheumatology in 2017 [10]. The classification of ILD and RPILD was based on the 2013 ATS/ERS diagnostic criteria for interstitial lung disease[11] and the diagnosis of progressive pulmonary fibrosis (PPF) was based on the 2022 ATS/ESR/JRS/ALAT Clinical Practice Guidelines [12, 13].

Statistical analysis

Continuous variables were presented as means ± standard deviation or median with interquartile range, and differences between survival and non-survival groups were compared using the Student's t-test or Mann Whitney U test. The Chi-square test or Fisher's Exact test was used to compare differences between categorical variables, which were reported as frequency and percentage. Univariate Cox regression was conducted and the factors showing $p < 0.05$ were included in the final multiple Cox model. The collinear variables of the baseline factors were excluded and Cox univariate regression analysis was performed for the remaining variables and outcome variables (survival status and follow-up time). The variables showing statistical significance ($P < 0.05$) in the univariate analysis were included in the Cox multivariate regression analysis. Backward rules were used to remove redundant variables and independent risk factors for death in anti-MDA5 antibody + DM-RPILD patients were identified.

Subsequently, a nomogram for predicting the 1-, 2- and 3-month overall survival(OS) was established, using the C-index to evaluate the discrimination ability of the nomogram. Time-dependent calibration was assessed using calibration curves with a bootstrap resampling method (bootstrap = 1000) at 1, 2, and 3 months. The optimal truncation values for continuous variables were calculated, which were divided into 2 groups using this optimal truncation value as the cut-off point. K-M survival analysis on both groups. Kaplan–Meier (K-M) curves were used to analyze the difference in survival between groups with cut-off values. To assess the clinical utility and practicality, decision curve analysis (DCA) curves were generated for the nomogram at 1, 2, and 3 months.

Results

Baseline data description

A total of 46 anti-MDA5 antibody + patients were admitted to the hospital, including 2 patients with RA, 1 patient with malignant lung tumor, and only 3 DM patients without ILD.The common clinical features of 3 DM patients without ILD were as follow: young age, rash or multiple arthritis as the main symptoms, chest CT showed no lung lesion, and elevated inflammatory markers. 2 patients received combination therapy including GCs and one immunosuppressant, 1 patient received two immunosuppressants without GCs. Their diseases all progressed slowly and prognosis were good. However, due to the small sample size, statistical analysis could not be carried out.

All the 40 patients of anti-MDA5 antibody + DM with ILD were enrolled and divided into two groups according to whether they died of ILD after the first diagnosis. The patients were followed up until August 2022 or death occured. The survival group included 17 patients with a median follow-up of 641 days. The non-survival group included 23 patients who were followed up of 31 days.

The age, DAD, LDH, CEA, ferritin, and CRP levels were significantly higher in the non-survival group compared to the survival group ($P < 0.05$), while the oxygenation index (PaO_2/FiO_2, P/F ratio) was higher in the survival group than in the non-survival group ($P < 0.05$). In addition, the two groups also showed statistically significant differences in the characteristics and extent of lung lesions and the treatment strategy, as shown in Table 1.

Analysis of prognostic factors

The statistical results of prognostic risk factors are shown in Table 2. The first column displays the results of the single-factor Cox regression analysis, the second column shows the results of the multi-factor Cox regression analysis, and the third column shows the results of the stepwise backward regression analysis. The results revealed that elevated ALT ($P = 0.043$), elevated LDH ($P = 0.044$), elevated CEA ($P = 0.002$), and elevated CRP ($P = 0.007$) were all risk factors for poor prognosis; the HR and 95% CI were 1.03 (1.00 1.06), 1.01 (1.00 1.01), 1.22 (1.08 1.38), and 1.04 (1.01 1.06), respectively. Compared with GCs alone and GCs combined with one immunosuppressant treatment, GCs combined with two immunosuppressants was a protective factor for patients ($P = 0.013$, HR 0.09, 95%CI (0.01–0.60). However, GCs alone and GCs combined with one immunosuppressant treatment showed no significant impact on the death of patients. Compared with patients without NSIP, patients with NSIP showed a 13.3 times higher risk of death ($P = 0.008$), with an HR and 95%CI of 13.30 (1.98–89.49).

The proportional risk hypothesis test for each covariate in the Cox model fitting showed no statistical significance ($P > 0.05$); moreover, the global test was not statistically significant ($P = 0.108$). Therefore, the Cox model conformed to the proportional risk hypothesis. The model C-index was 0.912 (se = 0.033), demonstrating high accuracy. In addition, the likelihood ratio was 49.89, the Wald test yielded 24.84, and the log-rank Index Score (log-rank) was 61.83.

After excluding the collinear variables of the baseline factors, Cox univariate regression analysis was performed for the remaining variables and outcome variables (survival status and follow-up time) one by one.

Table 1 General demographic data of patients with anti-MDA5 antibody + DM- ILD

Variable		Survival *N* = 17	Non-survival *N* = 23	*p*-value
Gender				0.747
Male		6 (35%)	10 (43%)	
Female		11 (65%)	13 (57%)	
Age		48 ± 14	56 ± 10	0.040
Smoker		1 (5.9%)	3 (13%)	0.624
Fever		4 (24%)	10 (43%)	0.315
Cough		7 (41%)	15 (65%)	0.200
Dyspnea		5 (29%)	14 (61%)	0.062
Clinical features	Pulmonary interstitial changes	3 (18%)	11 (48%)	0.092
	Pulmonary interstitial changes with rash	6 (35%)	4 (17%)	0.274
	Pulmonary interstitial changes with Joint & Muscle	1 (5.9%)	1 (4.3%)	> 0.999
	Pulmonary interstitial changes with Rash、Joint & Muscle	7 (41%)	7 (30%)	0.521
	Rash with itching	13 (76%)	13 (57%)	0.315
	Joint pain	5 (29%)	7 (30%)	> 0.999
P/F		350 (310, 399)	247 (185, 300)	0.006
Ro-52_antibody		12 (71%)	12 (52%)	0.332
RPILD (n,%)		7 (41%)	21(91%)	0.001
DAD		1 (5.9%)	9 (39%)	0.026
NSIP		1 (5.9%)	5 (22%)	0.216
OP		10 (59%)	14 (61%)	> 0.999
Mediastinal emphysema		1 (5.9%)	0 (0%)	0.425
Grid shadow		14 (82%)	17 (74%)	0.707
Extent of lung lesions				0.016
1		7 (41%)	5 (22%)	
2		10 (59%)	8 (35%)	
≥ 3		0 (0%)	10 (44%)	
Treatment				< 0.001
GCs		0 (0%)	9 (39%)	
GCs combined with one immunosuppressant		1 (5.9%)	7 (30%)	
GCs combined with two immunosuppressants		16 (94%)	7 (30%)	
WBC		4.77 ± 2.79	5.61 ± 2.40	0.325
Hb		121 ± 15	124 ± 23	0.604
N		3.50 ± 2.74	4.32 ± 2.18	0.317
L		0.90 ± 0.36	0.79 ± 0.28	0.293
D-Dimer		1,08(67, 1,68)	1,55(83, 2,22)	0.317
IgE		102 (35, 133)	72 (28, 136)	0.476
IgG		15.8 ± 3.2	15.1 ± 4.8	0.628
C3		0.91 ± 0.21	1.04 ± 0.24	0.099
ALT		25 (18, 55)	43 (30, 61)	0.238
AST		39 (32, 59)	57 (45, 99)	0.216
LDH		328 ± 101	433 ± 117	0.005
CK		81 (50, 133)	117 (54, 207)	0.159
GLU		32 (25, 48)	46 (27, 92)	0.029
AKP		70 (58, 81)	75 (59, 99)	0.142
ALB		32.6 ± 5.2	29.9 ± 3.8	0.078
ESR		33 ± 21	44 ± 24	0.165
PCT		0.05 (0.05, 0.10)	0.08 (0.05, 0.19)	0.082
Cre		39 ± 11	45 ± 13	0.193
CEA		2 (2, 3)	8 (4, 13)	0.002

Table 1 (continued)

Variable	Survival *N* = 17	Non-survival *N* = 23	*p*-value
Ferritin	569 (475, 766)	946 (673, 1362)	0.032
CRP	3 (3, 9)	13 (4, 49)	0.003
Follow-up	641 (343, 787)	31 (14, 63)	< 0.001

Table 2 Analysis of risk factors for death from anti-MDA5 + DM with ILD

Dependent:		All	HR (univariable)	HR (multivariable)	HR (final)
Gender		17 (51.5%)	0.76 (0.33–1.75, p = .513)		
Age		51.8 ± 12.0	1.03 (1.00–1.07, p = .081)		
DAD		7 (21.2%)	4.53 (1.89–10.89, p < .001)	0.79 (0.13–4.85, p = .802)	
NSIP		4 (12.1%)	3.47 (1.25–9.62, p = .017)	17.29 (1.51–198.45, p = .022)	13.30 (1.98–89.49, p = .008)
OP		21 (63.6%)	1.13 (0.49–2.61, p = .779)		
Reticular pattern		25 (75.8%)	0.59 (0.23–1.52, p = .275)		
Treatment	GCs alone or combined with one immunosuppressive agent	5 (15.2%)	0.46 (0.16–1.33, p = .153)	1.17 (0.13–10.55, p = .886)	1.24 (0.19–8.25, p = .824)
	GCs combined with two immunosuppressants	22 (66.7%)	0.10 (0.03–0.28, p < .001)	0.09 (0.01–0.71, p = .023)	0.09 (0.01–0.60, p = .013)
WBC		5.4 ± 2.7	1.07 (0.94–1.22, p = .317)		
Hb		123.6 ± 19.3	1.01 (0.99–1.03, p = .314)		
N		4.2 ± 2.6	1.07 (0.94–1.22, p = .297)		
L		0.8 ± 0.3	0.43 (0.12–1.63, p = .217)		
D-Dimer		2055.8 ± 2956.3	1.00 (1.00–1.00, p = .255)		
ALT		62.8 ± 108.9	1.00 (1.00–1.01, p = .022)	1.03 (1.00–1.06, p = .060)	1.03 (1.00–1.06, p = .043)
AST		100.1 ± 220.8	1.00 (1.00–1.00, p = .010)	0.99 (0.97–1.00, p = .056)	0.99 (0.97–1.00, p = .052)
LDH		391.4 ± 125.2	1.01 (1.00–1.01, p = .002)	1.01 (1.00–1.01, p = .033)	1.01 (1.00–1.01, p = .044)
CK		144.3 ± 140.6	1.00 (1.00–1.00, p = .339)		
GLU		69.9 ± 69.8	1.01 (1.00–1.01, p = .029)	1.00 (0.99–1.01, p = .487)	
AKP		86.9 ± 57.2	1.00 (1.00–1.01, p = .359)		
ALB		31.0 ± 4.4	0.93 (0.85–1.02, p = .131)		
CRE		43.6 ± 13.0	1.02 (0.98–1.05, p = .313)		
CEA		7.3 ± 8.5	1.16 (1.09–1.24, p < .001)	1.23 (1.08–1.40, p = .002)	1.22 (1.08–1.38, p = .002)
Ferritin		857.3 ± 619.4	1.00 (1.00–1.00, p = .078)		
CRP		17.2 ± 21.3	1.03 (1.01–1.04, p < .001)	1.04 (1.01–1.07, p = .008)	1.04 (1.01–1.06, p = .007)

Likelihood-ratio test = 50.64, *p* value < 0.001

The variables showing statistical significance ($P < 0.05$) in the univariate analysis were included in the Cox multivariate analysis. Backward rules ensured the removal of redundant variables to identify independent risk factors for death in patients with anti-MDA5 antibody + DM-ILD. Considering the close relationship between AST and ALT, they were also included, as shown in Fig. 2.

Evaluation of the prediction effect of COX regression

The "C-index" was calculated and the correction curve was drawn to evaluate the prediction effect of Cox regression. The analysis model's C-index was 0.912 (se = 0.033), which showing high accuracy.

The calibration chart for the OS of patients at 1 month, 2 months, and 3 months is shown below (Fig. 3). A larger overlap between the curve and the diagonal indicates a better model calibration.

A nomogram diagram was constructed according to the final multiple Cox model to predict the 1-, 2-, and 3-month OS (Fig. 4). The points for each prognostic factor could be obtained by the corresponding value on the vertical line. The total points for the nomogram were calculated by summing up the points from each

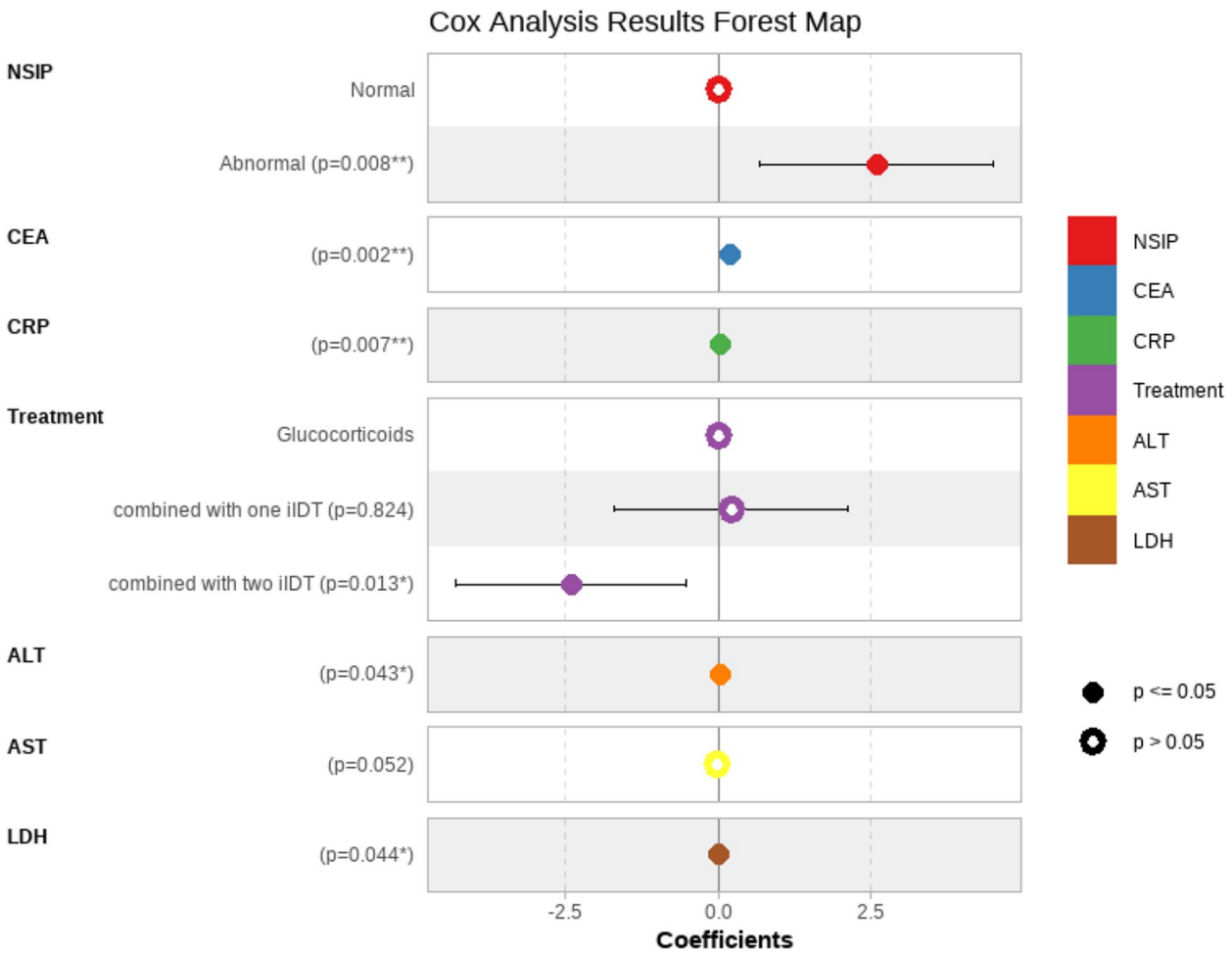

Fig. 2 Cox regression analysis forest map

prognostic factor. Finally, the 1-, 2-, and 3-month OS predictions were determined by drawing a vertical line from the total points axis and identifying the corresponding survival probability. But due to the small sample size, the estimated parameter range will become unstable, resulting in a wider confidence interval.

Each variable was marked on the corresponding line segment, which represents the range of values that the variable can take. The length of the line segment reflects the contribution of the factor to the outcome event. The single score corresponding to each variable under different values was shown in Fig. 4, and the total score was calculated by summing up of individual scores of each variable. The 1,2,3-month survival probability was shown below the graph.

Optimal cutoff value of continuous variables and K-M curve of each group

The continuous variables ALT, AST, LDH, CEA, and CRP were all included in the final model. According to the log-rank value of the continuous independent variable function of survival data, ALT = 25.00, AST = 39.00, LDH = 436.00, CEA = 3.17, CRP = 21.50 were used as the optimal cutoff values of the test index, and the above variables were divided into the high and low groups. The K-M algorithm was used to estimate the survival curve (Fig. 5). Except for ALT, the log-rank test values of the other indicators showed $p < 0.05$, indicating significant survival differences between the high and low groups.

DCA decision curve analysis

DCA curves were drawn for the two models; the model-dependent variables included treatment style, NSIP, ALT, AST, LDH, CEA, and CRP. One model employed a numerical variable fitting test index; in the other model, each numeric variable was truncated based on cut-off values. The following figure shows the DCA curve of the OS of patients at 30 days, 60 days, and 90 days (Fig. 6). The solid red line represents the numerical variable model, and the dotted green line

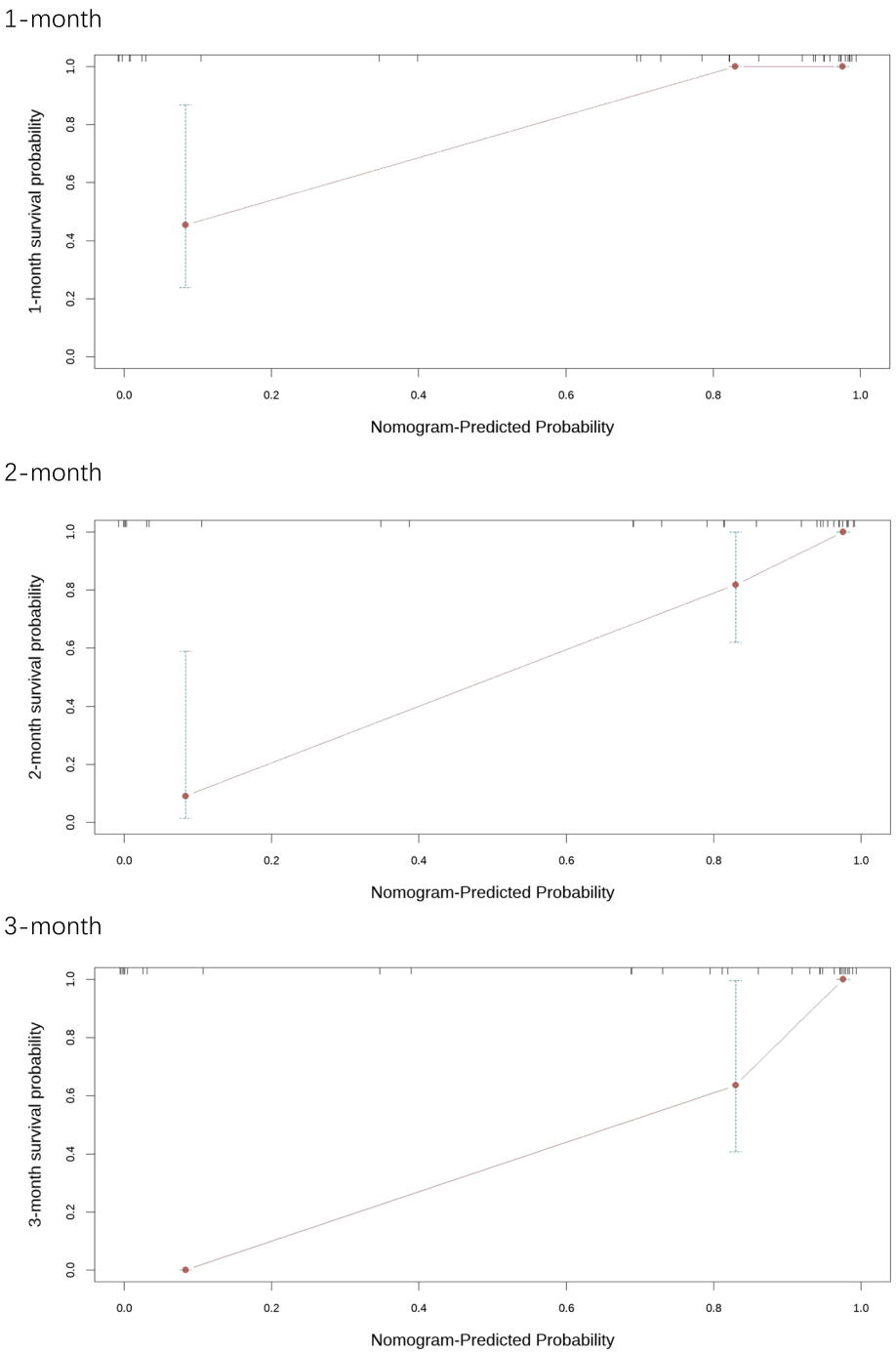

Fig. 3 Time-dependent (at 1-, 2-, and 3- months) calibration curve. Nomogram for visualization

denotes the grouping variable model. Comparing the two models, the closer the line is, the higher the clinical application value and the stronger the reference. The results indicate that the truncated value grouping model has better predictive value.

Discussion

MDA5 is widely expressed in the innate immune cells of the myeloid system. Its downstream signaling pathway activation can trigger innate and acquired immune responses, which play a vital role against infection.

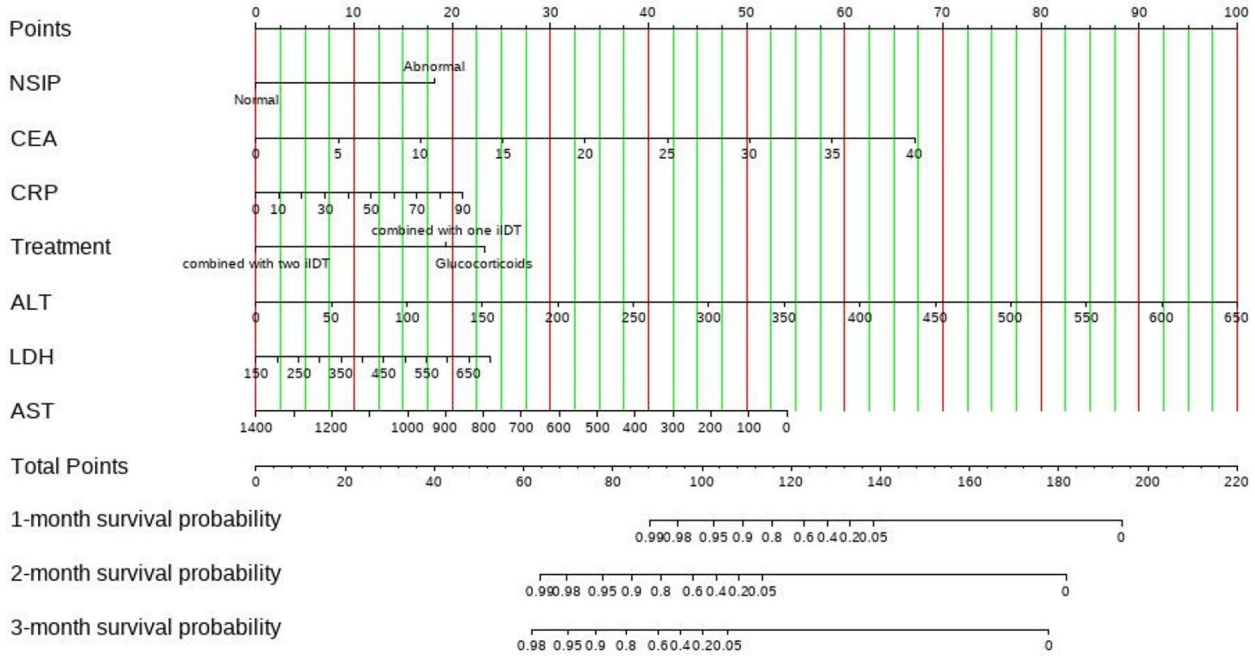

Fig. 4 Nomogram used to predict time-related recurrence. iIDT: intensive immunosuppressive drug treatment

Overexpression or DNA mutation of MDA5 can accelerate the production of anti-MDA5 antibodies, leading to a variety of autoimmune diseases [14, 15]. Previous studies have shown that positive anti-MDA5 antibodies have a sensitivity and specificity of 18% and 100% in DM diagnosis, respectively [16]. According to other studies, positive anti-MDA5 antibodies were only found in 10%−30% of DM patients [17, 18]. In our study, among 46 patients with positive anti-MDA5 antibodies, 43 cases were diagnosed with DM, accounting for 94%, indicating that anti-MDA5 antibodies have a certain diagnostic value for DM. ILD is the most common complication of anti-MDA5 antibody-positive DM, which is very likely to develope into RPILD with poor prognosis [16, 19, 20]. A meta analysis performed by our research team found that DM patients with positive anti-MDA5 antibody are more common in Asian women, with an incidence of ILD as high as 90%−95%[21]. In our study, the male to female ratio of DM patients with positive anti-MDA5 antibodies was 1:1.5, and ILD accounted for 93% [22, 23]. These findings suggested that ILD was often associated with anti-MDA5 antibody-positive DM. In addition, we reviewed the clinical data of three anti-MDA5 antibody+DM patients without ILD and found that the clinical features were different from those patients with ILD, and they all showed better clinical outcome. Previous studies had found certain heterogeneity in the clinical manifestations of DM patients with anti-MDA5 antibody positive. And several single-center and multi-center retrospective cohort studies have proposed three clinical phenotypes: the "rheumatoid type" characterized by arthritis and typical lesions, the "vascular type" characterized by Raynaud's phenomenon and severe vasculitis, and the "RPILD type" with a high mortality[24, 25].The phenomena observed in this study are consistent with previous studies, suggesting that accurate identification of patients' clinical subtypes is very critical to improving patient outcomes.

A growing number of studies have shown that the anti-MDA5 antibody titer in serum was significantly correlated with disease activity and death. Monitoring anti-MDA5 antibody and anti-Ro-52 antibody titer may contribute to predicting ILD occurrence, prognosis, and recurrence, thereby facilitating therapeutic evaluation [26–29]. In the present study, immunoblotting was performed to evaluate the anti-MDA5 antibody and anti-Ro-52 antibody titer, which were categorized into negative (-), weak positive (+), positive (++), and strong positive (+++). Among the 23 patients in non-survival group, 5 cases were weakly positive, 6 cases were positive, and 12 cases were strongly positive, which was consistent with previous studies. However, among the 17 patients in survival group, 3 cases were weakly positive, 2 cases were positive, and 12 cases were strongly positive. No significant difference was observed between anti-MDA5 antibody titer and risk of death. Furthermore, previous studies also have reported that presence of anti-Ro-52 antibodie was often accompanied by anti-MDA5 antibodie, resulting in an increased risk of ILD and a worse

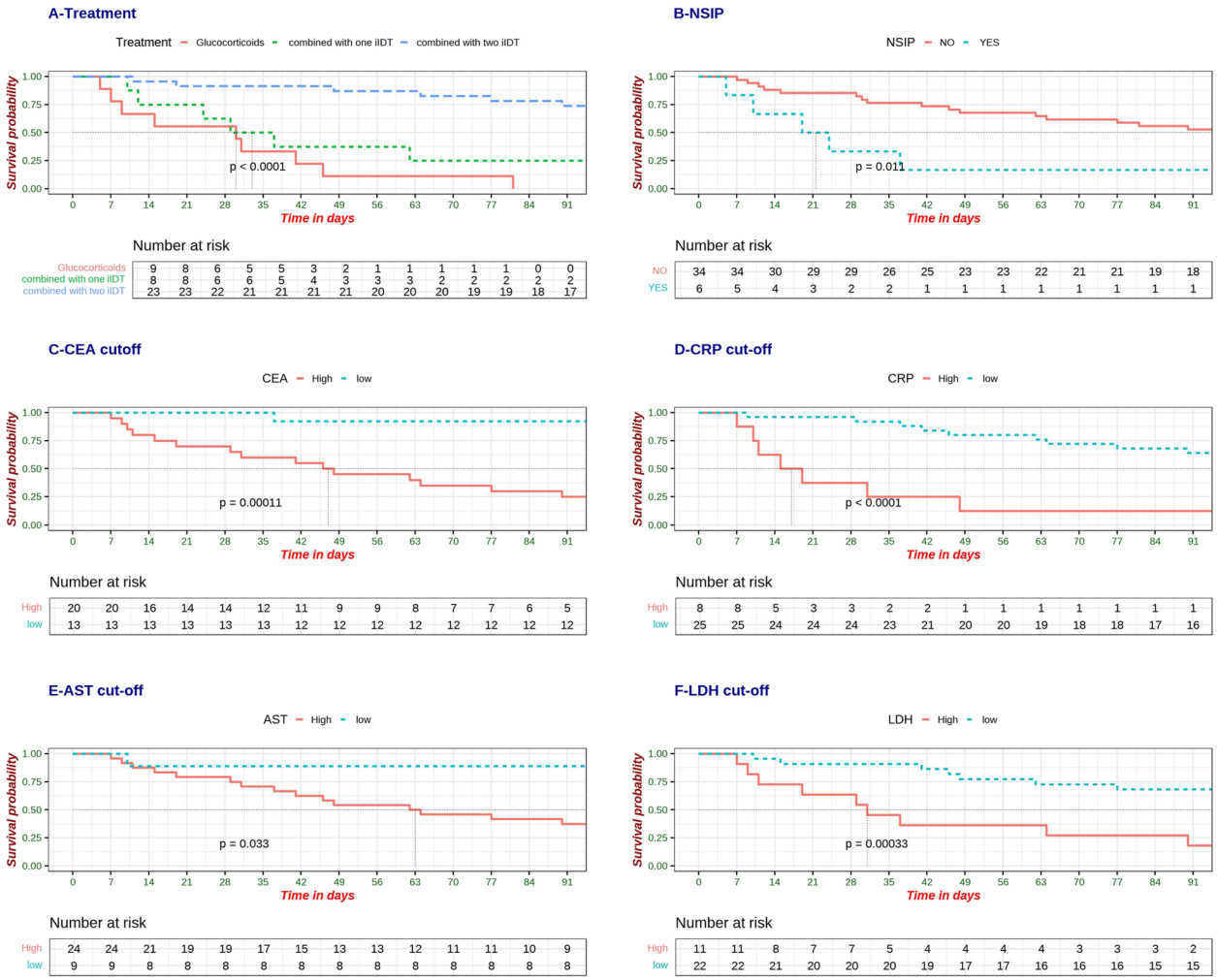

Fig. 5 The Kaplan–Meier curves

prognosis [4, 30, 31]. In our study, 24 cases were positive for anti-Ro-52 antibodies, including 11 in the non-survival group and 13 in the survival group, with no significant difference between the two groups (Supplement Table 1). Our results are not inconsistent with previous studies, which may be attributed to the small sample size. Although there was no statistical difference between the two groups in antibody titre, across both groups there was a high proportion of strong positive results and all the patients have RPILD, which need to be clarified certified in the future studies.

Motegi's study revealed that hypoxemia at the beginning of the disease was associated with RPILD and poor prognosis in anti-MDA5 + DM [32], which were similar to the results of our study. It has been shown that the severity of ILD patients with connective tissue diseases can be evaluated by the level of CEA[33]. Fahim et al. reported that serum CEA concentration was closely related to the severity of disease in patients with idiopathic pulmonary fibrosis [34]. Takahashi et al. also found that the increase of CEA in bronchoalveolar lavage fluid and serum from patients with idiopathic pulmonary fibrosis was related to the release of CEA after respiratory epithelial injury [35]. In our study, the CEA concentration in serum of patients with anti-MDA5 antibodies showed a significant increase in the non-survival group compared with the survival group. Furthermore, studies have shown that serum ferritin levels can not only be used as an indicator of DM activity but also as a prognostic indicator of DM-ILD, with ferritin levels ≥ 500 μg/L indicating much poorer prognosis[29, 36–38]. Our study showed that the ferritin and CRP level were significantly increased in all the anti-MDA5 antibody + DM patients with RPILD, indicating that anti-MDA5 antibody + DM patients with RPILD had a higher risk of inflammation and ferritin and CRP levels. Lymphocyte subgroup analysis can also reflect the immune system function of patients [39].

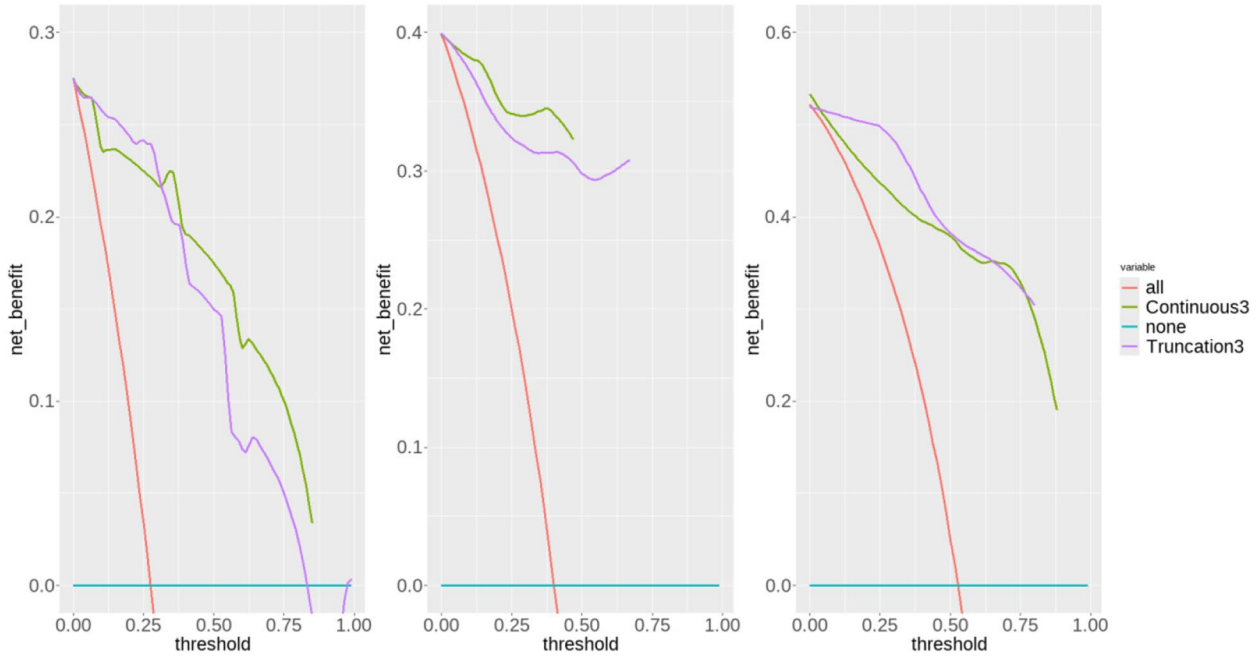

Fig. 6 Comparison of time-independent DCAs between the nomogram and independent risk factors. **A** 30-day DCA of nomogram; **B** 60-day DCA of nomogram; **C** 90-day DCA of nomogram. The red solid lines use the truncation value and the green dotted lines use the numeric variables. The DCA curves indicated that the nomogram yielded a higher net benefit compared to other single prognostic factors; the cutoff value grouping model showed better practical application value

In our study, the CD4 + T lymphocyte count in anti-MDA5 antibody-positive DM patients with PRILD was significantly lower than normal levels, but no significant difference was observed between the survival and non-survival groups ($P > 0.05$), which was aslo considered to be related to the small sample size. Our study also found that decreased serum ALB (< 30 g/L) was a predictor of poor prognosis, which may be attributed to the poor general condition of patients with more severe disease. In addition, elevated LDH (≥ 400 IU/L) was also a predictor of poor prognosis in patients, which may be related to inflammation and immune function abnormalities caused by muscle involvement and severe diseases [40, 41].

In the previous studies, lung histopathology of RPILD patients was primarily characterized by diffuse alveolar injury, including hyaline membrane formation, fibrin deposition, and pulmonary interstitial edema [18, 42]. In the present study, the radiographic characteristics of non-survival group mainly comprised diffuse alveolar injury, demonstrating a significant statistical difference from that of survival group ($P < 0.05$). Allen et al. divided 83 anti-MDA5 antibody-positive patients into three subgroups. The first group (18.1%) was associated with rapid ILD progression (93.3%) and a very high mortality rate, the second subgroup (55.4%) had simple skin rheumatism and better prognosis, and the third subgroup was mainly male (72.7%) with severe cutaneous vascular lesions and an intermediate prognosis [43, 44]. They considered that prognosis of anti-MDA5 antibody-positive patients with lung involvement was very poor, whereas the prognosis of patients with skin or joint muscle involvement was better. But this conclusion can not be drawn in our study because we mainly focused on the patients anti-MDA5 antibody + DM with ILD.

Currently, GCs are considered as the first-line treatment for anti-MDA5 antibody + DM patients with ILD, but no consensus has been reached regarding the dose, reduction plan, and course of treatment [43, 44]. In our study, all 40 patients were treated with methylprednisolone intravenous therapy after diagnosis, with a dose of 40-500 mg/d, which was gradually reduced after improvement, and then shifted to sequential oral therapy. A large number of studies have reported that early application of immunosuppressants may improve the prognosis of patients. Moreover, combined use of immunosuppressants with different mechanisms can reduce the duration and dose of GCs, thereby reducing the side effects [45, 46]. Due to the high rate of acute exacerbations and mortality associated with anti-MDA5 antibodies, combination therapy including GCs, multiple immunosuppressants, gamma globulin, and anti-fibrosis drugs was initiated at the early stage of treatment, after a comprehensive assessment of the patient's condition. Overall, 31 of the 40 initial

treatment patients received GCs combined with immunosuppressants (tacrolimus, mycophenolate mofetil, cyclophosphamide, baritinib, tofacitinib, tocilizumab, or rituximab). The detailed therapy and prognosis within 3 months were as follows: 9 patients were treated with GCs therapy alone, and 9 died; 8 patients were treated with GCs combined with 1 immunosuppressant, and 7 patients died. In addition, 23 patients were treated with combined with ≥ 2 immunosuppressants, and 7 patients died. Early initiation of combined drug therapy achieved a better therapeutic effect. This suggested that stronger immunosuppression may be associated with better outcomes.In this study, 15 of 40 patients were initially treated with gamma globulin 20 g/d for 3–5 days. For recent years, intravenous injection of gamma globulin was also found to be effective, with potential mechanism mainly through inhibiting Fc receptor up-regulation, replacing Fc receptor sites to reduce the half-life of endogenous immunoglobulin, neutralizing autoantibodies, and inhibiting complement activation, etc [47]. Overall, 10 of 40 patients were treated with the protein tyrosine kinase (JAK) inhibitor tofacitinib at a dose of 10 mg/day, which inhibits a variety of cytokines and molecules by inhibiting JAK1 and JAK3. The levels of interleukin-4, interleukin-6, and interleukin-10 decreased obviously in both groups after taking tofacitinib. Because of the signaling pathway of above molecules is mediated by JAK1 and JAK3, suggesting that tofacitinib is theoretically effective against anti-MDA5 antibody + DM with ILD [48, 49]. Clinical studies have revealed that tofacitinib can significantly improve the survival of CADM-ILD patients with anti-MDA5 antibody positive in the early stage [50, 51]. In addition, since pulmonary fibrosis often occur in the late stage of disease, anti-fibrosis therapy with pirfenidone or nintedanib may be also considered to delay the decline of lung function [42]. The optimal timing of drug intervention may also plays a crucial role in efficacy and treatment should be started as early as possible, especially before the onset of irreversible lung lesions. Due to the small sample size included in this study (Supplement Table 2), the treatment of patients with anti-MDA5 antibodies needs to be further evaluated in a large sample study.

Moreover, respiratory support is particularly important to those patients who had developed into RPILD. We analyzed all the respiratory support including oxygen therapy, noninvasive respiratory support, invasive respiratory support, and extracorporeal membrane oxygenation (ECMO). The distribution of respiratory support modes between the survival group and non-survival group was compared. The rank sum test analysis showed that $W = 1484.5$ and p-value < 0.0001, so there was significant difference in respiratory support modes between the two groups. Detailed data was shown in Supplement Table 3.

In conclusion, age, oxygenation index, characteristics (NSIP) and extent of lung lesions, elevated ALT, LDH, CEA, CRP in serum were all considered independent risk factors of poor prognosis in anti-MDA5 antibody + DM patients with ILD. The combined detection of LDH and CEA can predict survival and prognosis of anti-MDA5 antibody + DM patients with ILD. In this study, a predictive model was constructed based on prognostic risk factors proposed death alert values against MDA5 antibody + DM patients with ILD, which could help doctors make the appropriate treatment strategy. But this study is a single-center clinical study with a small sample size, which may lead to some result bias and certain limitations in the conclusions. Due to the complex mechanism and high mortality, furthermore multi-center clinical studies are needed in the further to optimize the prediction model, so as to determine early diagnosis, risk stratification, and make apporiate treatment strategy for anti-MDA5 antibody + DM patients with different clinical phenotypes.

Abbreviations

anti-MDA5 antibody + DM	Anti-MDA5 antibody-positive dermatomyositis
RPILD	Rapid progression of interstitial lung disease
DAD	Diffuse alveolar damage
NSIP	Nonspecific interstitial pneumonia
HRCT	High-resolution computed tomography
LDH	Lactic dehydrogenase
CEA	Carcinoembryonic antigen
CADM	Clinically amyopathic dermatomyositis
MSA	Myositis-specific antibody
DM	Dermatomyositis
SLE	Systemic lupus erythematosus
RA	Rheumatoid arthritis
CNIs	Calcineurin inhibitors
GCs	Glucocorticoids
CY	Cyclophosphamide
RTX	Rituximab
PE	Plasma exchange
A/SIP	Acute/subacute interstitial pneumonia
CIP	Chronic interstitial pneumonia
PaO_2	Arterial partial pressure of oxygen
FiO_2	Fraction of inspired oxygen
OP	Organized pneumonia
PPF	Progressive pulmonary fibrosis
NSIP	Nonspecific interstitial pneumonia
ECMO	Extracorporeal membrane oxygenation

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Authors' contributions
Kaikai Zhao and Juan Zhang collect the data and wrote the main manuscript, Qunyu Kong, Yong Zhang, and Cong Li mainly complete data analysis, Kaikai Huo, Na Fan, and Wenjing Deng prepared Table 1-2, Jie Shi, Chunya Wang and Xueyi Li prepared some figures, Shuanying Yang and Ping Fang modify the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The collection and review of the clinical data for this study and research implementation were approved by the Ethics Committee of the Second Affiliated Hospital, Xi'an Jiaotong University on 27 January 2023. All patients (or their guardians) included in the study were issued an informed consent form, which they read and understood before signing to indicate their full understanding of the research. The study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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