Predictors of mortality for dermatomyositis patients positive with anti-melanoma differentiation-related gene 5 and optimal treatment

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Abstract

Objective

To explore the risk factors of early death in dermatomyositis patients positive with anti-melanoma differentiation-related gene 5 antibody (anti-MDA5-DM). To explore the optimal treatment regimen for patients with anti-MDA5-DM.

Methods

Patients with newly onset anti-MDA5-DM from June 2018 to October 2021 in our centre were retrospectively reviewed for 6 months. Patients were divided into five groups based on initial treatments. The major outcome was mortality in 6 months. Secondary outcomes included remission and severe infection.

Results

A total of 214 patients were included in the study. During 6 month follow-up, 63 patients (30.14%) died, 112 patients (53.59%) achieved remission, 52 patients (24.88%) experienced serious infection and 5 patients (2.34%) were lost. Independent risk factors of mortality in the first 6 months after diagnosis were as follows: age>53 years, skin ulcer, peripheral blood lymphocyte count (LYMP)≤ 0.6×10^9/L, lactate dehydrogenase (LDH) >500 U/L, C reactive protein (CRP) >5mg/L, anti-Ro52 antibody and ground-glass opacity (GGO) score>2. On the contrary, prophylactic use of the compound sulfamethoxazole (SMZ Co) was independent protective factor. The five-category treatment was not an independent influencing factor of early death, but subgroup analysis found that patients with rapidly progressive interstitial lung disease (RPILD) responded better to a triple combination of high-dose glucocorticoids (GC), calcineurin inhibitors (CNI) and cyclophosphamide (CYC) or a triple combibation of GC, CNI and tofacitinib (TOF).

Conclusion

Advanced age, skin ulcer, lymphopenia, anti-Ro52 antibody and higher levels of LDH, CRP and GGO score incease the risk of early death for MDA5-DM, while prophylactic use of SMZ Co is protective. Aggressive therapy with combined immunosuppressants may improve the short-term prognosis of anti-MDA5-DM with RPILD.

Key words

anti-melanoma differentiation-related gene 5, dermatomyositis, prognosis, rapidly progressive interstitial lung disease

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Received on October 29, 2022; accepted on March 3, 2023.

Funding: the study was supported by grants from the National Natural Science Foundation of China [grant no. U1704177, 81871811], the Youth Project of Medical Science and Technology of Henan Provincial and Ministerial Joint Projects [grant no. 11551], the National High Level Hospital Clinical Research Funding [grant no. 2022-NHLHCRF-YS-02-05] and Elite Medical Professionals Project of China-Japan Friendship Hospital [grant no. ZRJY2021-GG14].

Competing interests: none declared.

Introduction

Dermatomyositis (DM) is a systemic autoimmune disease that often involves the skin, musculoskeletal system and lungs. Interstitial lung disease (ILD) is a major cause of death in patients with DM. When rapidly progressive ILD (RPILD) occurs, the mortality rate is significantly increased (1-6). Anti-MDA5 antibody was discovered in 2009 and is a risk factor for RPILD related mortality in DM patients (7, 8). Although not completely understood, data suggest that the pathogenesis of ILD in anti-MDA5-DM may be different from other types of DM (9). When RPILD occurs, about 80% of patients die (10). Intensive studies have been conducted on anti-MDA5-DM because of its low incidence and high mortality. To date, no guidelines have been available for optimal treatment of anti-MDA5-DM. Currently, the commonly-used regimens are the combination of high-dose GC and CNIs with or without cyclophosphamide (CYC) (11). While previous studies have demonstrated that the combination of tofacitinib (TOF) may significantly improve the prognosis of anti-MDA5-DM-related ILD (12-14), Tsuji *et al*. recommended a combination of GC with CYC and high-dose CNIs as the initial treatment (15).

We conducted this study to further explore the short-term risk factors related to prognosis of anti-MDA5-DM and the optimal treatments.

Patients and methods

Patients

The study included patients with newly onset anti-MDA5-DM admitted to the First Affiliated Hospital of Zhengzhou University from June 2018 to October 2021. The patient ages were defined as the age when the diagnosis was established. Patients with juvenile onset (n=1), overlapping diseases (n=6), co-existing infections (n=5) and coexisting malignancies (n=5) were excluded. Low-dose GC use (prednisone no more than 15 mg daily or its equivalents) within one month was allowed. A total of 214 patients were finally included and they were all Asians. All patients fully met the ENMC (16) as well as the Bohan and Peter criteria (17) for DM. All clinical data were obtained from our medical system. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2022-KY-0427).

Data collection

Data collection included demographic characteristics and clinical characteristics at baseline, treatment regimens, death and infection within six months. Anti-MDA5 antibody was determined by the same laboratory using ELISA kits (MBL, Japan). Anti-Ro52 antibody was determined using lining immunofluorescence (Euroimmun, Germany). GGO score was defined as the mean of five assessed lobe fields on high-resolution computed tomography (HRCT) using the method described by Kazerooni *et al*. (18). RPILD was defined as acute progressive dyspnoea and hypoxemia within 4 weeks from the onset of respiratory symptoms, accompanied by aggravation of ILD on HRCT (19). The disease activity of MDA5-DM was assessed according to physician's global assessment (PhGA) (assessed on a 10-cm visual analogue scale, with 0 representing no evidence of disease activity and 10 extremely active or severe disease activity) (20).

Treatment regimens

The main drugs of initial treatment included high-dose GC, CYC, CNIs, TOF, rituximab, etc. Secondary therapeutics included compound sulfamethoxazole (SMZ Co) and intravenous immunoglobulin (IVIG). High-dose GC was defined as 1–2 mg/kg/day initially. Prophylactic use of SMZ Co (each tablet contains 400 mg of sulfamethoxazole and 80 mg of trimethoprim) was defined as 200–800mg of sulfamethoxazole and 40–160mg of trimethoprim daily. All patients were treated with high-dose GC after diagnosis and most of them received immunosuppressants within one week. According to the initial treatments, patients were divided into five groups: Group A (GC + CYC + CNI, n=68), Group B (GC + TOF + CNI, n=33), group C (GC + CYC, n=28), group D (GC + CNI, n=30), and Group E (GC single or GC+other immunosuppressants, n=55).

Table I. Demographic manifestations, clinical features, laboratory results and GGO scores of the patients.

	Group A (n=68)	Group B (n=33)	Group C (n=28)	Group D (n=30)	Group E (n=55)	*p*-value
Demographic features						
Female, n (%)	45 (66.2)	25 (75.8)	15 (53.6)	24 (80.0)	36 (65.5)	0.213
Age, year, median (IQR)	51 (46-57)	49 (45-57)	52 (47-60)	52 (37-58)	56 (46-65)	0.156
Disease course, m, median (IQR)	2 (1-3)	2 (1-4)	2 (1-4)	3 (1-5)	2 (1-3)	0.505
Clinical features						
Myalgia, n (%)	18 (26.5)	9 (27.3)	7 (25.0)	12 (40.0)	10 (18.2)	0.305
Myasthenia, n (%)	21 (30.9)	8 (24.2)	5 (17.9)	12 (40/0)	14 (25.5)	0.372
Heliotrope sign, n (%)	54 (79.4)	29 (87.9)	24 (85.7)	25 (83.3)	40 (72.7)	0.416
Mechanic hand, n (%)	34 (50.0)	13 (39.4)	13 (46.4)	12 (40.0)	21 (38.2)	0.685
Gottron sign, n (%)	53 (77.9)	27 (81.8)	24 (85.7)	24 (80.0)	33 (60.0)	0.042
Periungual erythema, n (%)	7 (10.3)	4 (12.1)	8 (28.6)	2 (6.7)	4 (7.3)	0.082
Skin ulcer, n (%)	9 (13.2)	2 (6.1)	2 (7.1)	2 (6.7)	4 (7.3)	0.774
Arthritis, n (%)	33 (48.5)	16 (48.5)	15 (53.6)	22 (73.3)	29 (52.7)	0.217
Fever, n (%)	29 (42.6)	18 (54.5)	17 (60.7)	12 (40.0)	31 (56.4)	0.275
ILD, n (%)	68 (100.0)	33 (100.0)	28 (100.0)	30 (100.0)	53 (98.1)	0.687
RPILD, n (%)	31 (45.6)	10 (30.3)	9 (32.1)	5 (16.7)	27 (49.1)	0.021
Anti-Ro52, n (%)	43 (64.2)	17 (53.1)	20 (71.4)	17 (56.7)	37 (67.3)	0.528
KL-6, U/ml, median (IQR)	987 (582-1491)	730 (653-1059)	1061 (854-1354)	759 (515-1103)	942 (563-2168)	0.066
WBC, $\times 10^9$/L, median (IQR)	4.4 (3.6-6.0)	4.9 (3.8-7.1)	5.2 (3.8-6.5)	4.2 (3.0-6.4)	5.6 (4.0-6.9)	0.086
LYMP, $\times 10^9$/L, median (IQR)	0.7 (0.5-1.1)	0.8 (0.7-1.1)	0.8 (0.5-1.3)	0.7 (0.5-0.9)	0.8 (0.5-1.1)	0.675
ALB, g/L, mean (SD)	33.3 ± 5.2	34.8 ± 4.3	34.9 ± 3.9	34.3 ± 5.7	33.8 ± 5.0	0.206
LDH, U/L, median (IQR)	346 (281-453)	334 (293-417)	353 (285-407)	354 (267-449)	349 (280-562)	0.658
CK, U/L, median (IQR)	61 (39-121)	58 (33-168)	94 (60-163)	64 (39-139)	66 (41-131)	0.470
ESR, mm/h, median (IQR)	34 (17-48)	31 (18-49)	29 (19-59)	23 (15-39)	43 (22-64)	0.115
CRP, mg/L, median (IQR)	7.1 (3.1-17.9)	3.5 (1.5-17.5)	5.7 (1.3-14.6)	2.7 (1.1-5.2)	1.7 (3.1-29.0)	0.001
Ferritin, ng/ml, median (IQR)	850 (491-1639)	575 (192-1227)	1003 (340-1399)	537 (168-1785)	1109 (587-2108)	0.067
MDA5, U/ml, median (IQR)	185 (162-205)	170 (144-197)	182 (161-196)	182 (159-222)	170 (152-196)	0.181
GGO score, median (IQR)	1.5 (1.0-2.2)	1.3 (0.7-1.7)	1.5 (1.2-1.8)	0.9 (0.3-1.5)	2.2 (1.0-3.5)	0.001
PhGA score, median (IQR)	6.0 (5.0-7.0)	5.0 (5.0-6.0)	6.0 (5.0-7.0)	5.0 (3.0-5.0)	6.0 (5.0-9.0)	<0.001

Group A: glucocorticoid + cyclophosphamide + calcineurin inhibitor; Group B: glucocorticoid + tofacitinib + calcineurin inhibitor; Group C: glucocorticoid + cyclophosphamide; group D: glucocorticoid + calcineurin inhibitor; Group E: glucocorticoid single or glucocorticoid + other immunosuppressants.
RPILD: rapidly progressive interstitial lung disease; KL-6: Krebs von den Lungen-6; WBC: peripheral white blood cell count; LYMP: peripheral blood lymphocyte count; ALB: albumin; LDH: lactate dehydrogenase; CK: creatine kinase; ESR: erythrocyte sedimentation, CRP: C-reactive protein; anti-MDA5: anti-melanoma differentiation-associated protein-5; GGO: mean ground-glass opacity score per lung-lobe field; PhGA: The physician's global asessment of disease activity.

Outcomes

Primary outcome: death within 6 months. Other outcomes: remission and serious infections. Definition of remission: relief of clinical symptoms (not limited to respiratory symptoms), reduction or stabilisation of GGO score on HRCT, reduction of PhGA, and GC was tapered to no more than 15mg/day of prednisone or its equivelent. Severe infection was defined as infections required hospitalisation due to aggravated clinical symptoms or organ damage.

Statistical analysis

Categorical variables were described as percentages. Continuous variables were tested for K-S normality. Variables with normal distribution were described by mean ± standard deviation, and those with skewed distribution were described by median and quartiles. Continuous variables were converted to dichotomous variables, and cutoff values were set according to ROC analysis or medians, as appropriate.

Categorical variables were assessed by the Chi-squared test or Fisher's exact test. The predictive factors of death with $p<0.1$ in univariate analysis were included in the multivariate model. The treatment groups were introduced as a fixed variable, and other variables were selected by a forward stepwise (likelihood ratio) procedure based on the *p*-value. Data analysis was performed with SPSS (v. 26.0, USA). A *p*-value <0.05 was considered significant. GraphPad Prism (v. 6.0, USA) was used for graphing.

Results

Baseline features

Demographic manifestations, clinical features, laboratory results and GGO scores of the patients were recorded as Table I. The results showed that ILD (99.5%), heliotrope sign (80.4%), Gottron sign (75.2%), arthritis (53.7%) and fever (50.0%) were the most common clinical manifestations. Myalgia (26.2%) and myasthenia (28.0%) were less common and less severe. 134 patients (63.2%) were positive for anti-Ro52 antibody, and 82 patients (38.3%) experienced RPILD. These patients had higher levels of KL-6 [924 (612–1302)], serum ferritin [806 (394-1557)], LDH [346 (280–446)], ESR [32 (17–52)], CRP [5.8 (1.5–17.7)], GGO score [1.5 (0.9–2.2)], and lower levels of LYMP [0.8 (0.5–1.1)], ALB (33.8±5.1). The levels of CK were usually normal [56 (38–119)]. No significant differences in age, gender and disease duration were found between the five groups. Group D (GC+CNI) had a lower incidence of RPILD and lower levels of GGO and PhGA scores

than other groups (p=0.021, p=0.001, p<0.001).

Risk factors of early death

Univariate analysis showed that gender, myalgia, myasthenia, mechanic's hand, Gottron's sign, periungual erythema, creatine kinase level and MDA5 levels were not associated with 6-month mortality. Aged over 53 years, fever, skin ulcers, RPILD, leukocytes >7×10^9/L, lymphocyte counts ≤0.6×10^9/L, ALB ≤33 g/L, LDH>500U/L, KL-6 >1200U/mL), serum ferritin >600 ng/mL, ESR>30 mm/h), CRP >5mg/L and anti-Ro52 antibody were positively correlated with 6-month mortality, while disease duration >1month, heliotrope sign, arthritis and prophylactic use of SMZ Co were reversely associated with 6-month death. Compared with Group A, Group E had a higher risk of death within 6 months. The variables above were included in the multivariate model (Table II).

Independent risk factors of 6-month death included age >53y (OR: 7.205; 95% CI, 2.434–21.333, p<0.001), skin ulcer (OR: 5.857; 95% CI, 1.095–31.318, p=0.039), LYMP ≤0.6×10^9/L (OR: 3.697; 95% CI, 1.245–10.979, p=0.019), LDH >500U/L (OR: 5.406; 95% CI, 1.531–19.093, p=0.009), CRP >5 mg/L (OR: 5.637; 95% CI, 1.929–16.475, p=0.002), the positivity of anti-Ro52 antibody (OR: 6.505; 95%CI, 1.982–21.351, p=0.002) and GGO >2 (OR: 10.072; 95% CI, 3.070–33.043, p<0.001) (Table II, Fig. 1). Prophylactic use of SMZ Co was an independent protective factor of death within 6 months (OR: 0.068; 95% CI, 0.020–0.231, p<0.001). The five-category treatment was not an independent factor related to 6-month mortality in multivariate model (p=0.084).

Treatments and outcomes

Among the 214 patients, 63 patients (30.14%) died, 52 patients (24.88%) experienced severe infection, 112 patients (53.59%) achieved remission, and 5 patients (2.34%) were lost during the first 6 months.

For patients without RPILD, no significant difference was found in age, ge er, disease duration, GGO score and PhGA scores between five treatment groups. In addition, there was no significant difference between five groups in mortality, remission and severe infection (Table III, Fig. 2). The risk of mortality in Group B, C, D and E was not significantly increased than Group A (Fig. 3).

Table II. Initial parameters associated with early death using a logistic regression model.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age >53y	5.104	2.674-9.743	<0.001	7.205	2.434-21.333	<0.001
Disease course >1 month	0.368	0.200-0.675	0.001	–	–	–
Heliotrope sign	0.492	0.244-0.991	0.047	–	–	–
Skin ulcers	2.537	0.956-6.734	0.062	5.857	1.095-31.318	0.039
Arthritis	0.417	0.228-0.765	0.005	–	–	–
Fever	2.167	1.180-3.980	0.013	–	–	–
RPILD	4.024	2.160-7.495	<0.001	–	–	–
WBC >7× 10^9/L	3.109	1.518-6.367	0.002	–	–	–
LYMP ≤0.6 × 10^9/L	3.154	1.695-5.869	<0.001	3.697	1.245-10.979	0.019
ALB ≤33 g/L	6.957	3.536-13.687	<0.001	–	–	–
LDH >500 U/L	10.697	4.616-24.790	<0.001	5.406	1.531-19.093	0.009
ESR >30 mm/h	2.606	1.398-4.857	0.003	–	–	–
CRP >5 mg/L	7.181	3.388-15.220	<0.001	5.637	1.929-16.475	0.002
Serum ferritin >600 ng/ml	4.009	1.937-8.298	<0.001	–	–	–
KL-6 >1200 U/ml	3.535	1.886-6.623	<0.001	–	–	–
Anti-Ro52 positive	3.187	1.565-6.488	0.001	6.505	1.982-21.351	0.002
GGO > 2	9.673	4.865-19.230	<0.001	10.072	3.070-33.043	<0.001
Prophylactic use of SMZ Co	0.253	0.135-0.473	<0.001	0.068	0.020-0.231	<0.001
Five-category treatment (Compared with Group A)	–	–	0.018	–	–	0.084
Group B	0.631	0.208-1.916	0.416	3.438	0.511-23.138	0.204
Group C	1.871	0.695-5.037	0.215	6.480	1.436-29.253	0.015
Group D	0.964	0.331-2.807	0.946	0.711	0.120-4.231	0.708
Group E	3.805	1.739-8.328	0.001	2.202	0.594-8.164	0.238

Group A: glucocorticoid + cyclophosphamide + calcineurin inhibitor; Group B: glucocorticoid + tofacitinib + calcineurin inhibitor; Group C: glucocorticoid + cyclophosphamide; group D: glucocorticoid + calcineurin inhibitor; Group E: glucocorticoid single or glucocorticoid + other immunosuppressants. RPILD: rapidly progressive interstitial lung disease; WBC: peripheral white blood cell count; LYMP: peripheral blood lymphocyte count; ALB: albumin; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation, CRP: C-reactive protein; KL-6: Krebs von den Lungen-6; GGO: mean ground-glass opacity score per lung-lobe field.

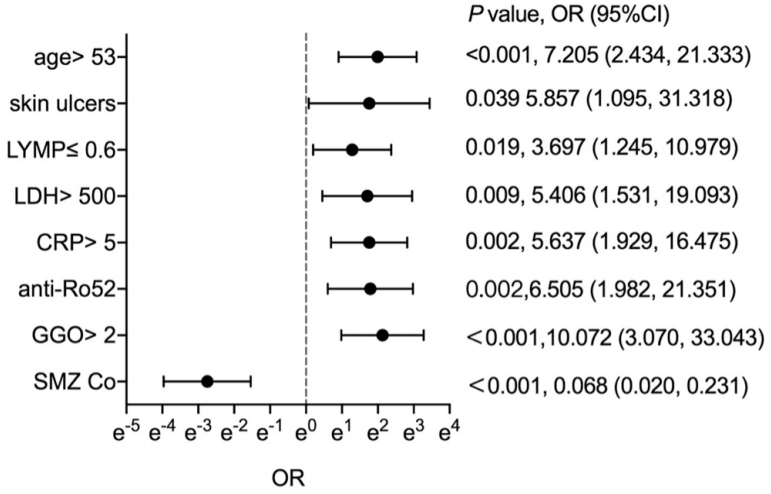

Fig. 1. Independent risk factors of death within 6 months.
In the multivariable model, candidate variables for inclusion included age (16-53, >53 years), disease course (0-1, >1 month), heliotrope sign, skin ulcers, arthritis, fever, RPILD, KL-6 (0-1200, >1200U/ml), WBC (0-7, >7x10^9/L), LYMP (0-0.6, >0.6x10^9/L), albumin (0-33, >33), ferritin (0-600, >600ng/ml), LDH (0-500, >500U/L), ESR (0-30, >30mm/h), CRP (0-5, >5mg/L), anti-Ro52, GGO (0-2, >2), prophylactic use of SMZ Co, five-category treatment regimen.

Table III. Outcomes of five groups at 6th month based on stratified RPILD.

	A (n=68)	B (n=33)	C (n=28)	D (n=30)	E (n=55)	*p*-value
Non-RPILD, n	37	23	18	23	27	–
Death, n (%)	6 (16.2)	3 (13.0)	4 (22.2)	4 (17.4)	7 (25.9)	0.797
Remission, n (%)	24 (64.9)	18 (78.3)	11 (61.1)	15 (65.2)	13 (48.1)	0.288
Severe infection, n (%)	6 (16.2)	3 (13.0)	4 (22.2)	6 (26.1)	4 (14.8)	0.775
RPILD, n	31	10	8	5	27	
Death, n (%)	9 (29.0)	2 (20.0)	5 (62.5)	2 (40.0)	21 (77.8)	<0.001
Remission, n (%)	16 (51.6)	5 (50.0)	3 (37.5)	2 (40.0)	5 (18.5)	0.093
Severe infection, n (%)	9 (29.0)	3 (30.0)	4 (50.0)	2 (40.0)	11 (40.7)	0.749

A: glucocorticoid + cyclophosphamide + calcineurin inhibitor; B: glucocorticoid + tofacitinib + calcineurin inhibitor; C: glucocorticoid + cyclophosphamide; D: glucocorticoid + calcineurin inhibitor; E: glucocorticoid single or glucocorticoid+ other immunosuppressants; RPILD: rapidly progressive interstitial lung disease.

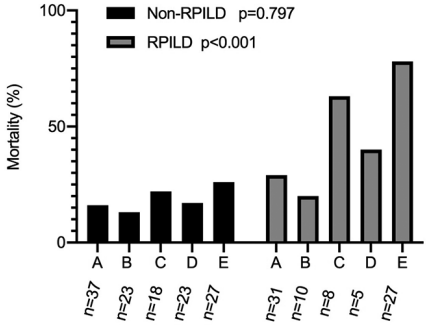

Fig. 2. Stratified mortality of five groups within 6 months.

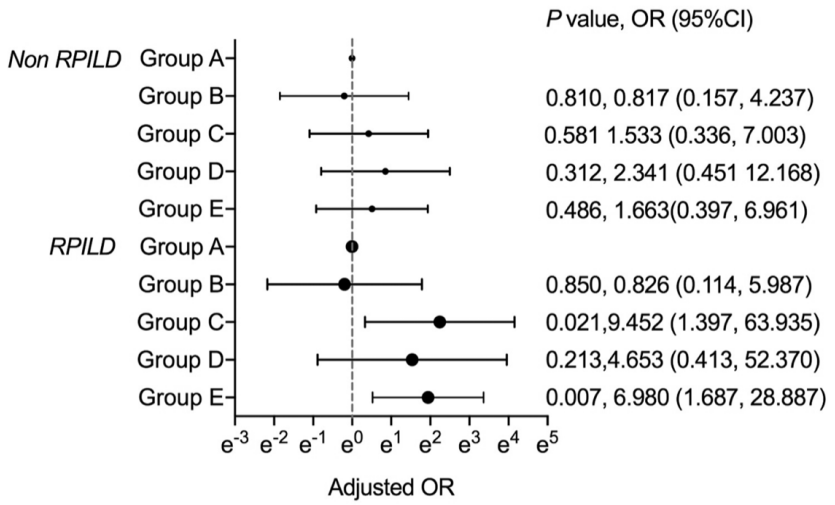

Fig. 3. Risk of mortality in different groups compared with Group A.
No significant difference was found in age, gender, disease duration, LYMP, albumin, ferritin and LDH between five groups both for patients with and without RPILD. For patients with RPILD, Group E had higher GGO and PhGA scores. The OR was adjusted by GGO and PhGA scores.

For patients with RPILD, Group E had a higher GGO score, PhGA score, and mortality. The rate of remission and severe infection were not significantly different between five groups. After adjusted by GGO and PhGA scores, the risk of mortality in Group B, C, D and E were 0.826 times (95% CI, 0.114–5.987, p=0.850), 9.452 times (95% CI, 1.397–63.935, p=0.021), 4.653 times (95% CI, 0.413–52.370, p=0.213) and 6.980 times (95% CI, 1.687–28.887, p=0.007) compared with Group A (Fig. 3).

Discussion

Reducing mortality of patients with anti-MDA5-DM poses a tremendous challenge to the rheumatology society. The predictors for prognosis may help physicians select optimal treatments. Our study suggest that advanced age, skin ulcer, lymphopenia, anti-Ro52 antibody and higher levels of LDH, CRP and GGO score incease the risk of early death for MDA5-DM, while prophylactic use of SMZ Co is protective. For patients without RPILD, both double combinations and triple combinations are effective and safe. In contrast, improved outcomes may be achieved in patients with RPILD with aggressive therapy with combined immunosuppressants.

A Japanese study has demonstrated that a triple combination of high-dose GC with CYC and CNI significantly may improve the prognosis of patients (14), but this study did not directly compare the efficacy of different combination regimens. Our conclusions are consistent with the Japanese study in that a triple combination of GC with CYC and CNI is effective in patients with and without RPILD with respect to reducing mortality and increasing remission rate. Nonetheless, this triple regimen was not superior to the combination of GC, tofacitinib and CNI. For patients with RPILD, the risk of mortality in Group C, D and E was increased compared to Group A. However, the difference between Group A and D was not significant, possibly due to the small number of cases in Group D. Given that both Group A (GC+CYC+CNI) and B (GC+TOF+CNI) have better performance than other groups, it is reasonable to hypothesize that the combination of immunosuppressive therapy and anti-inflammatory therapy may improve the short-term prognosis for anti-MDA5-DM patients.

Infection was the second leading cause of early death in our study. Prophylactic use of SMZ Co was a protective factor for early mortality in our study, which may be attributed by its efficacy in preventing infection. Based on these results, we strongly recommend the prophylactic use of SMZ Co in patients with anti-MDA5-DM.

The effects of IVIG on the short-time prognosis are controversial. A study

from our colleagues has demonstrated that initial treatment with IVIG may improve prognosis (21), but other colleagues in the same department did not reach the same conclusion (4). The study design and different treatments may be responsible for such discrepancy. Our results showed that patients treated with IVIG had high GGO scores than those without IVIG, therefore, we did not further explore the impact of IVIG.

Currently, it has been well accepted that RPILD is predictive for global prognosis and warrants aggressive treatment, which is not contradicted with our results. In our study, RPILD was associated with higher mortality at month 6. Patients with RPILD had an significantly advanced age, higher levels of KL-6, LDH, serum ferritin, ESR, CRP and GGO score at baseline. Besides, RPILD was well correlated with disease activity based on PhGA. However, it was not an independent risk factor of 6-month mortality, possibly due to its correlation with other variates.

Previous studies have shown that anti-Ro52 is a predictor for poor prognosis for anti-MDA5-DM patients (4, 22), consistently with our finding that anti-Ro52 was an independent risk factors of 6-month mortality.

The correlation of high-level serum ferritin and KL-6 with poor prognosis in anti-MDA5-DM (2, 4) have been reported by other groups, however, we did not find such significant correlation. Bivariate correlation analysis reveals a close correlation between ferritin with LDH and albumin. Similarly, KL-6 level is correlated with GGO scores. Therefore, ferritin and KL-6 are not considered as independent risk factors for short-term mortality.

Lyu *et al*. demonstrate that ages and increased Surfactant protein D (SPD) are prognostic for predicting 3-month mortality in patients with MDA5-ILD (23). In our study, advanced age is an independent risk factor of 6-month death. We did not explore the impact of SPD as the values are unavailable for most patients.

To the best of our knowledge, this is a real-world study including a large number of newly onset anti-MDA5-DM patients, and we expect that our findings may help clinician to make a prompt decision for optimal treatments in order to reduce early death of these patients.

The study also has some limitations. It is a single centre study, retrospective, and the follow-up period is relatively short. As it was not a randomised controlled clinical study, the caution should be taken when interpreting the results. More studies are needed to confirm our findings.

In conclusion, our study explores the risk factors of early death in anti-MDA5-DM patients, and confirms that agressive treatment may improve the short-term prognosis of anti-MDA5-DM with RPILD. These novel findings may help clinicians make prompt decision for optimal treatment for anti-MDA5-DM patients.

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