Triple-combination therapy did not improve prognosis in anti-MDA5 positive dermatomyositis: a multicentre longitudinal cohort study

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Abstract

Objective

Anti-melanoma differentiation-associated gene 5-positive dermatomyositis (MDA5+ DM) is frequently linked with interstitial lung disease (ILD), especially the rapidly progressive ILD (RP-ILD). We conduct this research to evaluate the efficacy and safety of triple-combination (triple-combo) therapy consisting of high-dose corticosteroids, tacrolimus and intravenous cyclophosphamide in treating MDA5$^+$ DM patients with ILD.

Methods

A multicentre longitudinal cohort study involving 115 MDA5$^+$ DM patients from the Nanjing Medical University Myositis Associated ILD (NMMI) cohort was conducted between January 2019 and November 2022. Patients were categorised into triple-combo and non-triple therapy groups, and their outcomes were assessed.

Results

Contrary to expectations, triple-combo therapy did not improve the prognosis for MDA5$^+$ DM patients but was linked to increased mortality rates, especially among those at high risk for RP-ILD.

Conclusion

Our study suggests that triple-combo therapy might not be effective in improving prognosis in MDA5$^+$ DM patients. Further research is needed to establish safer and more effective treatment modalities for this patient population.

Key words

anti-melanoma differentiation-associated gene 5, dermatomyositis, rapidly progressive interstitial lung disease, triple-combination therapy

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Introduction

Anti-melanoma differentiation-associated gene 5-positive dermatomyositis (MDA5+ DM) is frequently linked with interstitial lung disease (ILD), especially the rapidly progressive ILD (RP-ILD) (1, 2). Research suggests that 60-80% of MDA5+ DM develop ILD, and among them, approximately half will experience RP-ILD (3-6). Despite therapeutic interventions using immunosuppressive agents and corticosteroids, the 6-month mortality rate for MDA5+ DM patients with RP-ILD remains notably high, ranging from 50-70% (7-9). This resistance to treatment and poor prognosis have been ongoing challenges, prompting extensive research efforts to discover more effective treatment strategies for MDA5+ DM patients with RP-ILD.

Due to the rarity of MDA5+ DM, randomised controlled trials that address its treatment are lacking (2). Current treatment approaches for MDA5+ DM accompanied by ILD include glucocorticoids, which can be used either alone or in combination with immunosuppressive agents such as cyclophosphamide (CYC), mycophenolate mofetil, calcineurin inhibitors, tofacitinib, rituximab, and tocilizumab (1, 10). Due to the rapid deterioration commonly seen in RP-ILD, aggressive treatment strategies are often employed. One such regimen frequently recommended for early-stage RP-ILD is the "triple-combo" therapy, which consists of high-dose corticosteroids, a calcineurin inhibitor (tacrolimus, TAC), and intravenous CYC. Various studies and case reports have supported the efficacy of this triple-combo therapy in improving 6-month survival rates (11-16).

However, the majority of studies focusing on triple-combo therapy are retrospective and have a limited sample size. Despite this constraint, questions arise about the efficacy of triple-combo therapy *versus* dual-combo or monotherapies. A retrospective study in Japan found no significant survival advantage for triple-combo therapy over its alternatives (17). Further, combining two or more immunosuppressive agents was associated with an increased risk of opportunistic infections, such as herpes simplex virus/varicella-zoster virus and pneumocystis jirovecii pneumonia (PJP) (11, 18). For instance, one observational study indicated that the combined use of CTX and TAC significantly raised the risk of PJP infection (OR: 10.695), which in turn was linked to a higher mortality rate (18).

In light of these concerns, we assessed the efficacy and safety of triple-combo therapy in MDA5+ DM patients by drawing upon a relatively large cohort from the Nanjing Medical University Myositis Associated ILD (NMMI) cohort. The NMMI is an ongoing, multicenter observational and longitudinal cohort that aims to identify risk factors and outcomes associated with idiopathic inflammatory myopathy-associated ILD. Contrary to expectations, our analysis revealed that triple-combo therapy did not improve the prognosis for MDA5+ DM patients but was linked to increased mortality rates, particularly among those at high risk for RP-ILD.

Methods

Study design and population

A multicentre longitudinal cohort study of 115 inpatients from NMMI with newly diagnosed MDA5+ DM was conducted from January 2019 to November 2022. All of the participants fulfilled the DM criteria of Bohan and Peter (19), or Sontheimer's criteria of clinically amyopathic DM (20). Myositis-specific autoantibodies (MSAs) (antigens including MDA5, Jo-1, PL-7, PL-12, EJ, and OJ), and myositis-associated antibodies (MAAs) (antigens including Ku, Ro-52, PM-Scl 100, and PM-Scl 75) of all the patients were measured using Euroline immunoassays (Euroimmun) by the same central laboratory. Clinical data of all patients were recorded, including demographic data, including gender, age, and disease course; clinical features, including muscle weakness, Gottron papules/heliotrope rash/V sign/shawl sign/periungual erythema, arthritis, mechanic's hand, and skin ulcers/vasculitis; laboratory features, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), ESR and CRP, as well as causes of death.

The time of the first hospital visit was defined as the baseline. All clinical data was collected from baseline (initially diagnosed as DM) to death or the last follow-up visit. Two expert thoracic radiologists re-examined all available HRCT imaging from baseline to death or the last follow-up visit. Clinical data and CT scans were then obtained at 1- to 3-month intervals. Diagnosis and assessment of ILD and RP-ILD were consistent with those in our previous studies (21). Briefly, RPILD was defined as the acute and progressive worsening of dyspnea onset within one month, with the presence of any of the following four conditions: 1) acute and progressive worsening of dyspnea requiring hospitalisation or supplementary oxygen; 2) lung function including forced vital capacity (FVC) decreases by more than 10%, or diffusion capacity for carbon monoxide of the Lung (DLCO) falls over 15% with the decreased FVC; 3) HRCT of the chest demonstrates that the extent of interstitial abnormalities increased more than 20%; 4) arterial blood gas analysis suggests respiratory failure or the oxygen partial pressure reduction is greater than 10 mmHg. Exclusion criteria include (i) patients with other autoimmune diseases including systemic lupus erythematosus, systemic sclerosis, and rheumatoid arthritis; (ii) patients with lung cancer and chronic pulmonary disease, including occupational-environmental exposures and chronic obstructive pulmonary disease; (iii) patients with concomitant COVID pneumonia.

In our study, MDA5+ DM patients with ILD who were treated with a combined immunosuppressive regimen from baseline (high-dose GCs, tacrolimus, and IV CYC) were defined as the initial triple therapy group. Tacrolimus was adjusted to maintain a 12-hour blood trough level of 10–12 ng/mL. IVCY was initiated at 500 mg/m^2 of body surface area (BSA) biweekly, then gradually increased to a maximum dose of 1,000 mg/m^2 of BSA according to a nadir leukocyte count from baseline. Patients who were treated with one-kind of immunosuppressive regimen (tacrolimus, mycophenolate mofetil, or IV CYC) with or without high-dose GCs were defined as non- triple therapy group. This study was approved by the Ethical Committee of the First Affiliated Hospital of Nanjing Medical University: 2020-SR-265.

Table I. Clinical characteristics of patients at baseline in triple-combination therapy group and non-triple therapy group.

	Total (n=115)	Triple therapy (n=24)	Non-triple therapy (n=91)	*p*
Age, mean±SD, years	51.39 ± 13.62	47.63 ± 14.96	52.38 ± 13.15	0.128
Course of the disease, median (range), months	2 (1, 6)	2 (1, 3.75)	3 (1, 6)	0.172
Follow-up periods, median (range), months	8 (3, 21)	7 (3, 14.25)	8 (3, 23)	0.377
male, n. (%)	45 (39.13%)	10 (41.67%)	35 (38.46%)	0.775
Myasthenia, n. (%)	42 (36.52%)	11 (45.83%)	31 (34.07%)	0.287
Gottron papule, n. (%)	60 (52.17%)	11 (45.83%)	49 (53.85%)	0.485
Heliotrope rash, n. (%)	58 (50.43%)	11 (45.83%)	47 (51.65%)	0.612
V sign, n. (%)	38 (33.04%)	7 (29.17%)	31 (34.07%)	0.65
Shawl sign, n. (%)	26 (22.61%)	4 (16.67%)	22 (24.18%)	0.434
Skin erythema, n. (%)	42 (36.52%)	8 (33.33%)	34 (37.36%)	0.715
Raynaud's phenomenon	4 (3.48%)	0 (0%)	4 (4.4%)	0.296
Periungual erythematosus, n. (%)	31 (26.96%)	11 (45.83%)	20 (21.98%)	0.019*
Arthritis, n. (%)	32 (27.83%)	6 (25%)	26 (28.57%)	0.728
Mechanic's hands, n. (%)	38 (33.04%)	13 (54.17%)	25 (27.47%)	0.013*
Superficial erosion and ulcer, n. (%)	17 (14.78%)	4 (16.67%)	13 (14.29%)	0.77
Anti-MDA5 antibody				
Low titre (+), n. (%)	27 (23.48%)	2 (8.33%)	25 (27.47%)	
Moderate titre (++), n. (%)	24 (20.87%)	9 (37.5%)	15 (16.48%)	
High titre (+++), n. (%)	63 (54.78%)	12 (50%)	51 (56.04%)	
Anti-Ro52 antibody				0.503
Low titre (+), n. (%)	28 (24.35%)	7 (29.17%)	21 (23.08%)	
Moderate titre (++), n. (%)	15 (13.04%)	1 (4.17%)	14 (15.38%)	
High titre (+++), n. (%)	33 (28.7%)	8 (33.33%)	25 (27.47%)	
CTX, n. (%)	30 (26.09%)	24 (100%)	6 (6.59%)	<0.001*
TAC, n. (%)	87 (75.65%)	24 (100%)	63 (69.23%)	0.008*
MMF, n. (%)	4 (3.48%)	1 (4.17%)	3 (3.3%)	0.836
JAK, n. (%)	14 (12.17%)	3 (12.5%)	11 (12.09%)	0.956
LEF, n. (%))	1 (0.87%)	(0%)	1 (1.1%)	0.606
Nintedanib, n. (%)	12 (10.43%)	4 (16.67%)	8 (8.79%)	0.262
Pirfenidone, n. (%)	5 (4.35%)	1 (4.17%)	4 (4.4%)	0.961
Cluster 1, n. (%)	39 (42.9%)	8 (33.3%)	47 (40.9%)	0.476
Cluster 2, n. (%)	29 (31.9%)	7 (29.2%)	36 (31.3%)	
Cluster 3, n. (%)	23 (25.3%)	9 (37.5%)	32 (27.8%)	

*Values statistically significant at $p<0.05$.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) for normally distributed data and median and interquartile range (P25, P75) for all other data. The Kolmogorov-Smirnov test was used to test for normal distribution. Categorical variables are presented as numbers (percentages). Student t-tests or Mann-Whitney U-tests were used to evaluate the association between normally distributed variables and endpoint events. The Chi-square test or Fisher's exact test was used to evaluate for categorical variables, as appropriate.

Using unsupervised analyses and decision tree reported before (21), we identified 3 subgroups that can be interpreted as follows: mild risk of RP-ILD for cluster 1, moderate risk of RP-ILD for cluster 2, and high risk of RP-ILD for cluster 3 (21). Cumulative survival rates were compared using Kaplan-Meier analysis, and the log-rank test was used to test for significant differences between groups. To account for potential confounding by indication, we performed propensity score adjustment and used inverse probability of treatment weighting (IPTW) to estimate the treatment effect of triple therapy to RPILD and death. Balance of the covariates after IPTW was assessed using standardised mean differences (SMD) and kernel density plots. We then calculated stabilised IPTWs for use in the survival analysis. The *p*-value was two-

Table II. Laboratory characteristics of patients at baseline in the triple-combination therapy group and non-triple therapy group.

	Total (n=115)	Triple therapy (n=24)	Non-triple therapy (n=91)	*p*
White blood cell, median (range), 10^9/l	5 (3.66, 7.17)	5.56 (3.66, 7.38)	4.95 (3.63, 7.12)	0.988
Lymphocyte, median (range), 10^9/l	0.85 (0.58, 1.09)	0.68 (0.52, 0.94)	0.87 (0.6, 1.17)	0.045*
Monocyte, median (range), 10^9/l	0.47 (0.29, 0.62)	0.45 (0.29, 0.64)	0.47 (0.3, 0.59)	0.868
Neutrophile granulocyte, median (range), 10^9/l	3.58 (2.46, 5.52)	4.38 (2.59, 6.65)	3.5 (2.39, 4.98)	0.227
PLT, mean±SD, 10^9/L	192.81 ± 72.49	186.85 ± 85.49	194.17 ± 69.69	0.685
ALT, median (range), units/L	43 (28.8, 76.9)	43 (30.8, 72.7)	43.4 (27.13, 77.8)	0.983
AST, median (range), units/L	49.6 (31, 76.7	51 (30, 114)	49.45 (31.43, 71.9)	0.782
LDH, median (range), units/L	306.5 (249.75, 395.25)	334 (263, 428)	294 (246.5, 372.5)	0.146
CK, median (range), units/L	42 (27, 111.75)	86 (27, 275)	39 (27, 104)	0.106
ESR, mean±SD, mm/h	33.94 ± 22.92	32.17 ± 20.02	34.4 ± 23.71	0.68
CRP, median (range), mg/L	4.6 (2.24, 10.93)	6.3 (1.95, 17.8)	4.27 (2.3, 10.6)	0.508
Ferritin, median (range), ng/mL	638.3 (216.6, 1083.8)	975.5 (421.3, 1698.6)	552.7 (172.65, 941.6)	0.018*
AFP, median (range), ng/mL	2.26 (1.45, 4.04)	1.8 (0.97, 3.45)	2.3 (1.48, 4.09)	0.157
CEA, median (range), ng/mL	3.48 (2.1, 6)	2.36 (0.77, 4.91)	3.95 (2.35, 6.36)	0.052
Ca-199, median (range), U/mL	10.03 (4.19, 19.12)	10.6 (1, 17.69)	9.9 (4.78, 19.16)	0.706
Ca-724, median (range), U/mL	1.11 (0.69, 2.6)	1.03 (0, 1.58)	1.17 (0.72, 2.8)	0.205
CYFRA21-1, median (range), ng/mL	2.95 (2.04, 4.33)	2.88 (1.07, 4.19)	3.02 (2.04, 4.33)	0.761
NSE, median (range), ng/mL	17.91 (13.52, 22.18)	14.78 (9.01, 26.51)	18.42 (13.86, 21.97)	0.442
CA125, median (range), U/mL	7.2 (0, 12.43)	8.1 (0, 13.8)	6.5 (0, 12.2)	0.325
Fbg, median (range), g/L	3 (2.48, 3.69)	3.07 (2.53, 3.87)	2.97 (2.45, 3.63)	0.683
D-Dimer, median (range), mg/L	0.77 (0.47, 1.6)	0.98 (0.39, 2.06)	0.77 (0.51, 1.46)	0.842
IgG, median (range), g/L	13 (10.8, 15.8)	14 (11.4, 16.8)	12.65 (10.5, 15.5)	0.179
IgA, mean±SD, g/L	2.79 ± 1.26	2.69 ± 1.05	2.82 ± 1.31	0.662
IgM, median (range), g/L	1.23 (0.9, 1.74)	1.11 (0.76, 1.44)	1.25 (0.92, 1.89)	0.106
C3, mean±SD, g/L	0.86 ± 0.18	0.87 ± 0.18	0.82 ± 0.16	0.298
C4, median (range), g/L	0.22 (0.19, 0.31)	0.26 (0.2, 0.32)	0.22 (0.19, 0.29)	0.244
LY%, mean±SD	15.81 ± 10.37	15.18 ± 7.76	15.91 ± 10.79	0.831
CD3+%, mean±SD	62.88 ± 23.2	72.5 ± 11.41	60.37 ± 24.85	0.048*
CD4+%, mean±SD	42.12 ± 18.16	47.11 ± 14.35	40.68 ± 18.96	0.164
CD8+ %, mean±SD	19.8 ± 12.49	24.77 ± 14.14	18.35 ± 11.69	0.043*
CD19+%, mean±SD	19.38 ± 13.29	16.75 ± 10.89	20.14 ± 13.89	0.317
NK%, mean±SD	6.23 ± 5.13	6.98 ± 5.37	6.03 ± 5.08	0.486

*Values statistically significant at $p<0.05$.

Table III. Incidence of RP-ILD and mortality in the triple-combination therapy group and non-triple therapy group.

	RP-ILD		*p*	Death		*p*
	Triple therapy (n=24)	Non-triple therapy (n=91)		Triple therapy (n=24)	Non-triple therapy (n=91)	
Total, n (%)	13 (54.17%)	23 (25.27%)	0.007*	12 (50%)	23 (25.27%)	0.019*
0-3 months, n (%)	13 (54.17%)	22 (24.18%)	0.005*	9 (37.5%)	15 (16.48%)	0.006*
3-6 months, n (%)	0 (0%)	1 (1.1%)	-	2 (8.33%)	4 (4.4%)	0.538
>6 months, n (%)	0 (0%)	0 (0%)	-	1 (4.17%)	4 (4.4%)	1

*Values statistically significant at $p<0.05$.

tailed and defined as significant if the value was <0.05. SPSS software, v. 23 (Chicago, IL, USA) and R v. 4.3 were used for all of the statistical descriptions, analyses and inferences.

Results

Study cohort and demographics

We recruited 115 patients with MDA5+ DM from the NMMI cohort, of which 24 received triple therapy and 91 non-triple therapy. Forty-five cases (39.13%) were male, and the average age of all subjects was 51.39±13.62 years, with a median disease course of 2 months and a median follow-up period of 8 months. During the median 8 months of follow-up (interquartile range: 3–21 months), 36 (31.3%) patients developed RP-ILD, and the overall mortality was 30% (35/115). Their clinical features at baseline are described in Tables I and II.

Clinical characteristics and laboratory findings

The triple therapy group exhibited a higher incidence of periungual erythema and mechanic's hands ($p<0.05$). However, there were no significant disparities in other baseline clinical characteristics between the two groups, including age, sex, disease course, rash, and arthritis. In laboratory tests, the triple therapy group had lower lymphocyte counts and elevated ferritin levels ($p<0.05$). No other significant differences were observed in laboratory indicators (Table II). As expected, the usage of cyclophosphamide and

tacrolimus was more prevalent in the triple therapy group.

Comparative outcomes of triple therapy vs. non-triple therapy

We assessed the outcomes for patients receiving initial triple therapy *versus* those undergoing non-triple therapy. In the triple therapy group, both the incidence of RP-ILD (54.17% *vs.* 25.27%, p=0.007) and mortality rates (50% *vs.* 25.27%, p=0.019) were significantly higher compared to the non-triple therapy group. When categorising MDA5+DM patients into three subgroups based on disease onset time, a significantly higher incidence of RP-ILD (54.17% *vs.* 24.18%, p=0.005) and mortality (37.5% *vs.* 16.48%, p=0.006) was noted in the triple therapy group at the first 3 months post-onset (Table III). No differences were found in subsequent timeframes.

The presence of RP-ILD may influence the therapeutic decisions of physicians, leading to a preference for triple therapy. To minimise the impact of baseline disease severity on treatment outcomes, we also conducted separate analyses for patients with and without RP-ILD. The clinical characteristics of patients with and without concurrent RP-ILD are presented in Supplementary Tables S1 and S2. We found that the use of triple therapy did not improve mortality outcomes, with no significant difference in mortality rates between triple therapy and non-triple therapy groups in patients with (p=0.841) or without RP-ILD (p=0.340). These results are presented in Supplementary Tables S3-S6.

Efficacy of triple therapy in high RP-ILD risk subgroups

We aimed to determine if initial triple therapy offered benefits to high-risk RP-ILD patients. Patients were stratified into three RP-ILD risk subgroups: cluster 1 (low risk), cluster 2 (medium risk), and cluster 3 (high risk), utilising a previously established decision-tree classification method (21). As anticipated, patients in cluster 3 exhibited the highest incidence rates of RP-ILD and mortality when compared to clusters 1 and 2. Specifically, the triple therapy group in cluster 3 had a significantly higher incidence of RP-ILD (100% *vs.* 45.45%, p=0.011) and mortality (89.5% *vs.* 40.1%, p=0.024) (Table IV and V). Notably, although did not reach a statistical difference, initial triple-therapy increased the trend of death risk in the low-risk subgroup of cluster 1 (42.86% *vs.* 17.14%, p=0.13).

Table IV. Clinical characteristics of patients at baseline in different clusters.

	Cluster 1 (n=43)	Cluster 2 (n=34)	Cluster 3 (n=29)	*p*
Age, mean±SD, years	50.94 ± 14.61	48 ± 11.64	55.88 ± 13.34	0.055
Course of the disease, median (range), months	4 (2, 7)	3 (2, 4)	1 (1, 2)	0.52
Male, n. (%)	19 (40.43%)	17 (47.22%)	9 (28.13%)	0.266
Myasthenia, n. (%)	17 (36.17%)	10 (27.78%)	15 (46.88%)	0.263
Gottron papule, n. (%))	26 (55.32%)	19 (52.78%)	15 (46.88%)	0.759
Heliotrope rash, n. (%)	21 (44.68%)	20 (55.56%)	17 (53.13%)	0.579
V sign, n. (%)	18 (38.3%)	11 (30.56%)	9 (28.13%)	0.595
Shawl sign, n. (%)	10 (21.28%)	9 (25%)	7 (21.88%)	0.916
Skin erythema, n. (%)	17 (36.17%)	15 (41.67%)	10 (31.25%)	0.671
Raynaud's phenomenon	2 (4.26%)	0 (0%)	2 (6.25%)	0.347
Perilungual erythematosus, n. (%)	13 (27.66%)	11 (30.56%)	7 (21.88%)	0.716
Arthritis, n. (%)	11 (23.4%)	20 (55.56%)	1 (3.13%)	<0.001*
Mechanic's hands, n. (%)	13 (27.66%)	13 (36.11%)	12 (37.5%)	0.59
Superficial erosion and ulcer, n. (%)	8 (17.02%)	5 (13.89%)	4 (12.5%)	0.843
Anti-MDA5 antibody				0.068
Low titre (+), n. (%)	16 (34.04%)	7 (19.44%)	4 (12.5%)	
Moderate titre (++), n. (%)	9 (19.15%)	11 (30.56%)	4 (12.5%)	
High titre (+++), n. (%))	21 (44.68%)	18 (50%)	24 (75%)	
Anti-Ro52 antibody				0.003*
Low titre (+), n. (%)	7 (14.89%)	11 (30.56%)	10 (31.25%)	
Moderate titre (++), n. (%)	4 (8.51%)	5 (13.89%)	6 (18.75%)	
High titre (+++), n. (%)	9 (19.15%)	13 (36.11%)	11 (34.38%)	
CTX, n. (%)	12 (25.53%)	8 (22.22%)	10 (31.25%)	0.695
TAC, n. (%)	34 (72.34%)	30 (83.33%)	22 (68.75%)	0.339
MMF, n. (%)	2 (4.26%)	1 (2.78%)	1 (3.13%)	0.928
JAK, n. (%)	7 (14.89%)	5 (13.89%)	2 (6.25%)	0.478
LEF, n. (%)	1 (2.13%)	0 (0%)	0 (0%)	0.482
Nintedanib, n. (%)	1 (2.13%)	5 (13.89%)	6 (18.75%)	0.043*
Pirfenidone, n. (%)	2 (4.26%)	1 (2.78%)	2 (6.25%)	0.782
RP-ILD, n. (%)	8 (17.02%)	13 (36.11%)	15 (46.88%)	0.015*
Death, n. (%)	8 (17.02%)	12 (33.33%)	15 (46.88%)	0.016*

*Values statistically significant at p<0.05.

Adjusted clinical outcomes

To control for clinical parameter variations between the two treatment groups, we employed IPTW to adjust lymphocyte count, ferritin level, periungual erythematosus, mechanic's hands. Figure 1 shows the SMD between the triple therapy and non-triple therapy groups before and after IPTW. Table VI displays the adjusted incidence and mortality rates of RP-ILD across different clusters. Notably, triple therapy did not reduce but rather increased the incidence and mortality of RP-ILD in cluster 3 after IPTW adjustment (p<0.05). Survival analysis revealed no significant differences in RP-ILD incidence and mortality rates between the triple therapy and non-triple therapy groups (Fig. 2 A-B). This finding persisted even after IPTW adjustment (Fig. 2 C-D).

Discussion

MDA5+ DM is a clinically heterogeneous disease with high incidence RP-ILD and mortality. Some studies have indicated that intensive therapy during the early stages following diagnosis could lead to improved prognoses (22, 23). Although there is no standardised therapy recommended for managing MDA5+ DM, a 'triple-therapy' consisting of high-dose corticosteroids, TAC, and CYC is widely used, particularly for individuals at high risk of RP-ILD. However, this treatment proves refractory in many cases, with a reported overall mortality rate of 40% after treatment (24). In addition to its partial effectiveness, triple therapy is associated with various adverse events,

Table V. Laboratory characteristics of patients at baseline in different clusters.

	Cluster 1 (n=43)	Cluster 2 (n=34)	Cluster 3 (n=29)	*p*
White blood cell, median (range), 10^9/l	4.68 (3.63, 7.15)	5.17 (3.51, 7.42)	5.32 (3.98, 7.38)	0.947
Lymphocyte, median (range), 10^9/l	0.85 (0.57, 1.09)	0.82 (0.58, 1.22)	0.86 (0.56, 1.08)	0.472
Monocyte, median (range), 10^9/l	0.46 (0.3, 0.56)	0.43 (0.28, 0.64)	0.48 (0.3, 0.67)	0.542
Neutrophile granulocyte, median (range), 10^9/l	3.57 (2.19, 4.96)	3.79 (2.58, 6.39)	3.61 (2.81, 5.52)	0.445
PLT, mean±SD, 10^9/L	193.84 ± 69.28	204.54 ± 82.73	177.67 ± 63.3	0.33
ALT, median (range), units/L	31.7 (18.75, 53.3)	56.2 (31.5, 107.1)	52.1 (30.5, 97.9)	0.042*
AST, median (range), units/L	39.9 (25.25, 62.15)	54.8 (32.1, 84.1)	51.3 (33.3, 98.9)	0.101
LDH, median (range), units/L	271 (230, 345)	286.5 (258, 376)	345 (308, 499)	0.233
CK, median (range), units/L	37 (27.5, 90)	42.5 (27.5, 104.75)	54 (27, 209)	0.042*
ESR, mean ± SD, mm/h	32 ± 24.02	34.63 ± 22.51	36.03 ± 22.22	0.743
CRP, median (range), mg/L	3.55 (2.03, 7.2)	4.43 (2.24, 7.94)	10.28 (2.82, 20)	0.108
Ferritin, median (range), ng/mL	451.6 (100, 853.4)	782.3 (219.33, 1060.23)	870.75 (511.53, 1391.16)	0.08*
AFP, median (range), ng/mL	2.21 (1.64, 3.69)	2.15 (0.96, 4.07)	2.67 (1.36, 4.27)	0.604
CEA, median (range), ng/mL	3.45 (2.05, 5.99)	3.1 (1.5, 5.02)	5.06 (2.29, 10.88)	0.02*
Ca-199, median (range), U/mL	10.12 (6.18, 19.55)	9.9 (1.18, 16.32)	8.2 (3.98, 20.27)	0.552
Ca-724, median (range), U/mL	1.13 (0.78, 3.35)	1.14 (0.69, 2.67)	0.98 (0.67, 2.53)	0.505
CYFRA21-1, median (range), ng/mL	3.02 (2, 3.86)	2.95 (2.05, 4.57)	2.84 (1.96, 5.15)	0.454
NSE, median (range), ng/mL	15.56 (13.65, 19.39)	19.79 (16.8, 24.66)	17.98 (12.81, 24.06)	0.658
CA125, median (range), U/mL	6 (0, 12.2)	0 (0, 9.2)	10.05 (0, 18.4)	0.014*
Fbg, median (range), g/L	2.97 (2.33, 3.63)	3.36 (2.55, 4.05)	2.74 (2.33, 3.52)	0.601*
D-dimer, median (range), mg/L	0.67 (0.39, 1.39)	0.63 (0.44, 1.69)	1.17 (0.58, 2.3)	0.325
IgG, median (range), g/L	11.4 (9.48, 15.25)	13.8 (11.68, 15.9)	13.5 (10.7, 17.1)	0.311
IgA, mean ± SD, g/L	2.7 ± 1.32	2.88 ± 0.85	2.82 ± 1.56	0.829
IgM, median (range), g/L	11.4 (9.48, 15.25)	1.2 (0.95, 1.55)	1.25 (0.89, 1.97)	0.594
C3, mean ± SD, g/L	0.86 ± 0.18	0.88 ± 0.18	0.84 ± 0.17	0.735
C4, median (range), g/L	0.23 (0.19, 0.31)	0.22 (0.19, 0.3)	0.25 (0.2, 0.28)	0.968
LY%, mean ± SD	17.87 ± 11.17	13.05 ± 8	13.85 ± 6.4	0.339
CD3+%, mean ± SD	66.55 ± 20.35	69.6 ± 54.6	65.81 ± 50.83	0.431
CD4+%, mean ± SD	45.02 ± 16.91	44.55 ± 30.2	44.75 ± 31.81	0.446
CD8+ %, mean ± SD	22.05 ± 12.48	17.6 ± 12.09	14.35 ± 10.2	0.359
CD19+%, mean ± SD	19.57 ± 12.76	14.9 ± 8.85	20.35 ± 13.58	0.417
NK%, mean ±SD	5.47 ± 3.93	6.2 ± 2.55	4.8 ± 1.53	0.107

*Values statistically significant at $p<0.05$.

Table VI. RPILD and mortality in different groups before and after IPTW.

		Unadjusted			IPTW		
		Non-triple therapy	Triple therapy	*p*	Non-triple therapy	Triple therapy	*p*
Total	RP-ILD	25.27%	54.17%	0.007*	28.24%	55.00%	0.022*
	DEATH	25.27%	50.00%	0.019*	25.29%	60.00%	0.002*
Cluster =1	RP-ILD	15.38%	25.00%	0.51	17.14%	14.29%	0.853
	DEATH	15.38%	25.00%	0.51	17.14%	42.86%	0.13
Cluster =2	RP-ILD	31.03%	57.14%	0.197	31.03%	60.00%	0.211
	DEATH	27.59%	57.14%	0.137	27.59%	40.00%	0.574
Cluster =3	RP-ILD	34.78%	77.78%	0.028*	45.45%	100.00%	0.011*
	DEATH	39.13%	66.67%	0.16	40.91%	87.50%	0.024*
Cluster =2, 3	RP-ILD	32.69%	68.75%	0.01*	36.00%	76.92%	0.008*
	DEATH	32.69%	62.50%	0.033*	34.00%	75.00%	0.01*

For each cell, the categories and shades of color represent the percentages (%) of RP-ILD or death in each group. Colour codes indicate the highest percentage in red (100%), and the lowest percentage in green (0%).
IPTW: inverse probability of treatment weighting. *Values statistically significant at $p<0.05$.

primarily infections and alterations in renal function. Incidences of bacterial, viral, and fungal infections have been reported, such as herpes simplex virus/varicella-zoster virus and PJP (11, 15, 18, 25). The alteration in renal function is mainly attributed to calcineurin inhibitors and often results in treatment interruptions.

The studies on triple therapy mentioned above mainly stem from studies with small sample sizes. In this study, we assessed the impact of triple therapy on 115 MDA5+ DM patients. Our findings revealed that triple therapy does not prevent development or progression of RP-ILD and mortality in MDA5+ DM patients. When we categorised MDA5+ DM patients into low, medium, and high RP-ILD risk subgroups, it became evident that early intense therapy with the triple-drug combination could not prevent RP-ILD onset or improve mortality rates among those at high risk for RP-ILD. Furthermore, even in the low and medium RP-ILD subgroups, the relatively favorable prognoses subgroup, triple therapy showed an upward trend of RP-ILD incidence and mortality, albeit without significant differences.

Two potential explanations underlie these findings. First, within our dataset, approximately one-third of MDA5+ DM patients develop RP-ILD. The mechanisms driving this progression remain

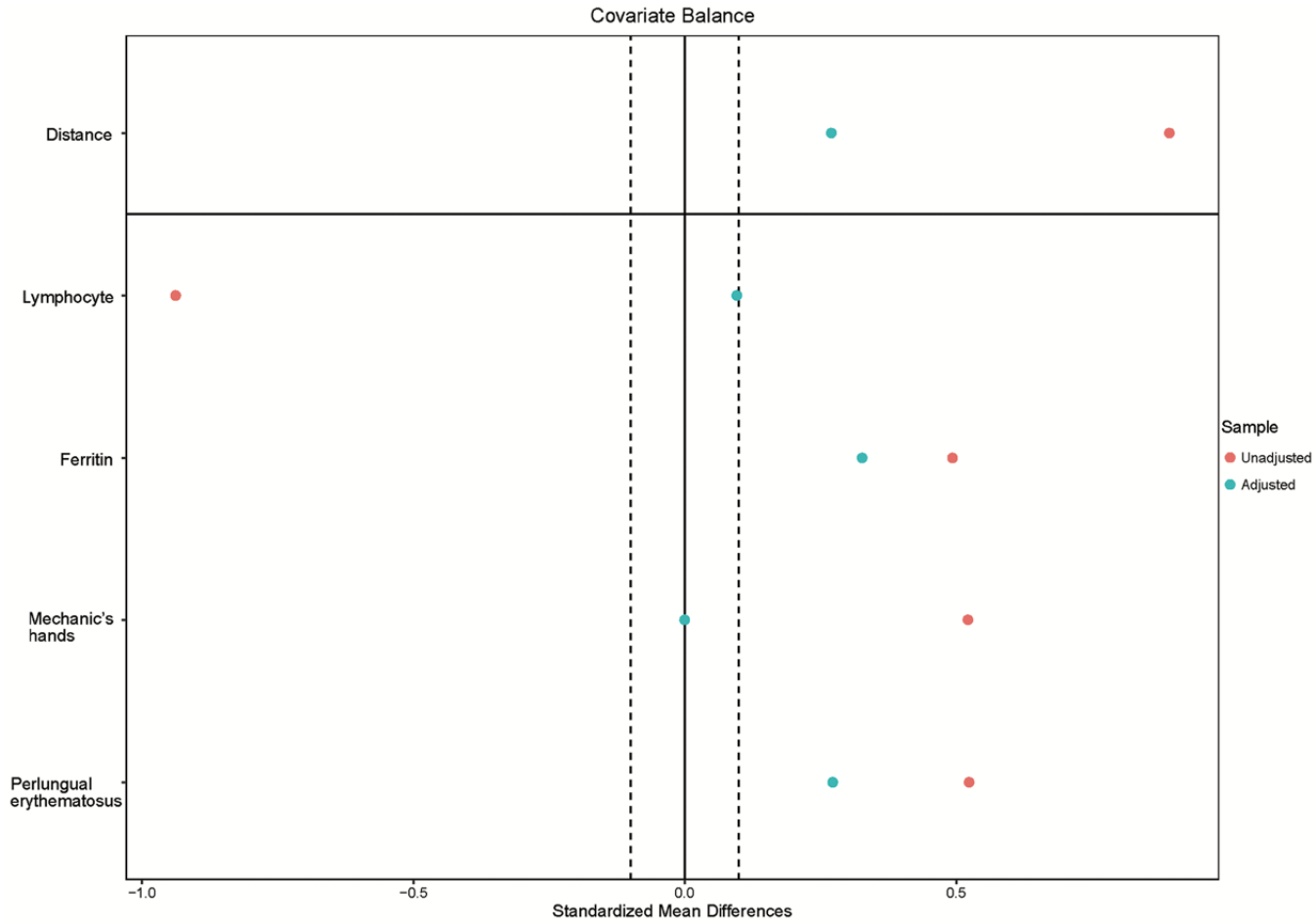

Fig. 1. The standardised mean difference (SMD) before and after inverse probability of treatment weighting (IPTW) adjustment. To balance the differences between treatment and control groups, we adjusted lymphocyte count, neutrophil count, and ferritin level using IPTW. The red circle represents the SMD before adjustment, and the blue triangle represents the SMD after IPTW.

elusive. Recent comprehensive single-cell studies suggest strong activations of antibody-secreting cells and CD8+ T cell responses, along with type I interferon signalling, as pivotal immune features of MDA5+ DM (26). Although calcineurin inhibitors primarily target T cells, triple therapy cannot fully target the key pathogenic pathways of RP-ILD development which could contribute to its failure in preventing disease progression.

Second, an alternative interpretation is that triple therapy might heighten the risk of infection, thereby exacerbating prognosis. Nevertheless, this study did not quantify infection rates across different groups, a subject that we intend to investigate further in subsequent studies. In light of these findings, we propose that the triple combination of corticosteroids, TAC, and CYC may not be an ideal strategy for managing MDA5+ DM. Prudent caution should be exercised, especially when treating MDA5+ DM patients without a high risk of rapidly progressive RP-ILD.

This study also has certain limitations. First, because the four centres in our study are all tertiary hospitals, the patients are relatively severe, and there is a patient selection bias. Secondly, the small number of patients with triple therapy may have affected some of the statistical results, but the conclusions drawn in this study are also expected. In the future, randomised controlled trials with larger samples are needed to explore the therapeutic value of triple therapy in MDA5+ DM. Last but not least, although the differences may sometimes not be significant, the triple-combination therapy group had more cluster 3 patients, and higher laboratory abnormalities (LDH, ferritin, CRP) than non-triple combination therapy group. It seemed that the triple-combination therapy should be adapted to more severe disease. The IPTW method we used in the article can adjust some differences between groups. Moreover, as this is a longitudinal cohort observational study, clinicians tend to opt for triple therapy in patients with more severe conditions. Therefore, the patients in the triple therapy group inherently have more severe conditions, which leads to patient selection bias. We analysed the efficacy of triple therapy in both patients with and without RP-ILD and found that it did not improve patient mortality rates in either group. This, to some extent, corroborates our conclusion, even in the presence of certain patient selection bias. In the future, more randomised controlled trials are needed to further validate our findings.

Overall, this study revealed that triple

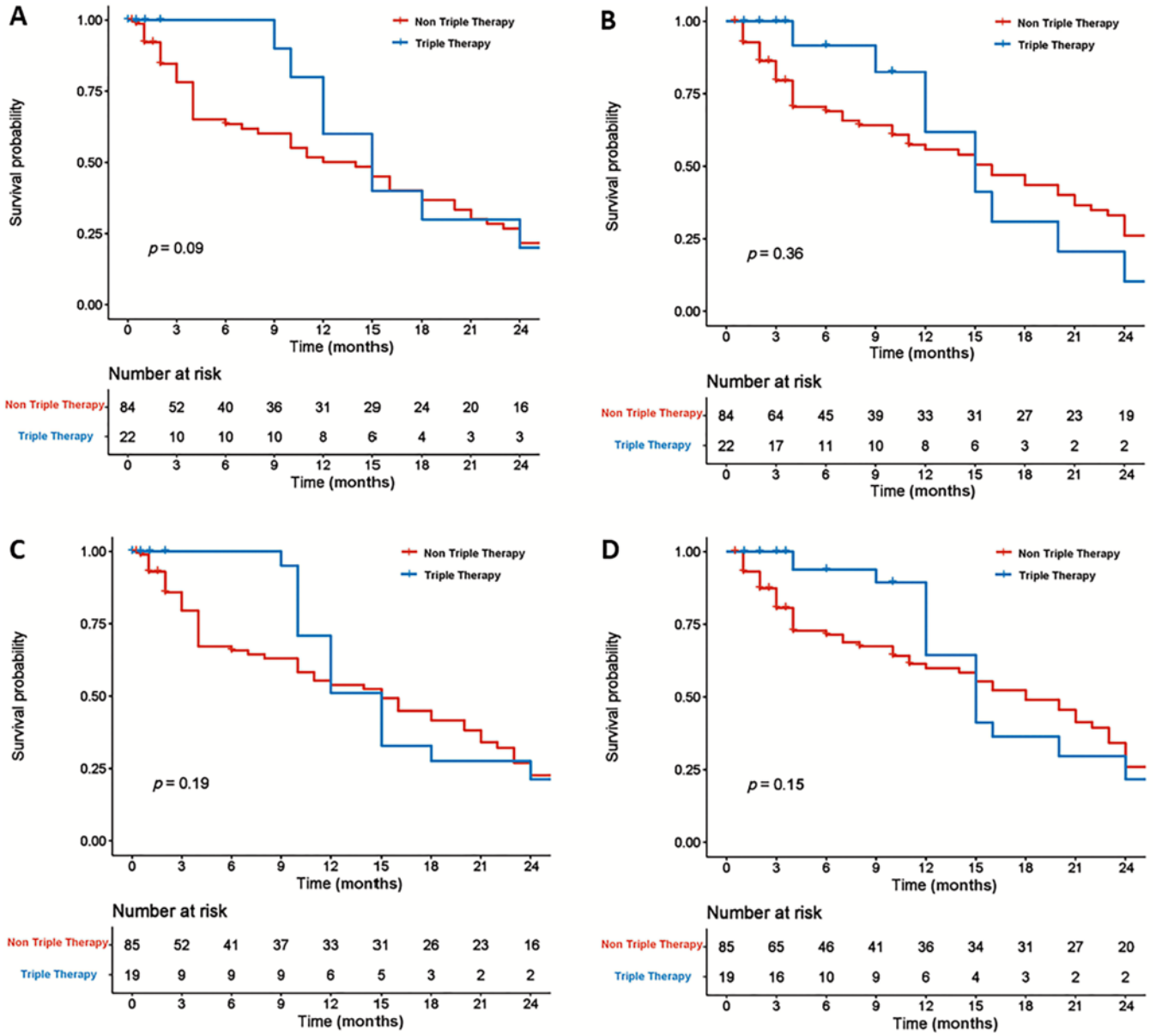

Fig. 2. Survival analysis showed no significant difference in the incidence of RP-ILD (2A) and the incidence of death (2B) between the triple-combination therapy group and the non-triple therapy group. Survival analysis showed no significant difference in the incidence of RP-ILD (2C) and the incidence of death (2D) between the triple-combination therapy group and non-triple therapy group after IPTW.

therapy failed to improve the prognosis of MDA5+DM patients and, in fact, led to an elevated incidence and mortality of RP-ILD, particularly among high-risk patients. Before initiating triple therapy, it is imperative to engage in a thorough discussion of potential benefits and risks with a healthcare provider. Furthermore, it is essential to recognise that triple therapy does not constitute the standard of care for all patients diagnosed with MDA5+ DM and may not be suitable for every individual. Treatment decisions should be tailored on a case-by-case basis, taking into account a variety of factors including symptom severity, concurrent medical conditions, and individual preferences. Further research is needed to establish safer and more effective treatment modalities for the MDA5+ DM patient population.

Take home messages

- The presence of RP-ILD in MDA5+ DM is associated with high mortality.
- Triple-combo therapy does not improve the prognosis for MDA5+ DM patients.
- Alternative treatment strategies are urgently needed.

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