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Investigation of poor prognostic factors in patients with asymptomatic dermatomyositis

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Purpose: To clarify poor prognostic factors associated with mortality and respiratory dysfunction in clinically amyopathic dermatomyositis (CADM).
Methods: CADM patients treated with induction remission therapy at Kitasato University Hospital from 2013 to 2021 were included. Factors associated with prognosis were analyzed retrospectively.
Results: Thirty-one CADM (24 female) were 57.0 years old (median, IQR 47.0－67.0). The common factors associated with mortality (n = 8) and poor respiratory dysfunction (n = 10) were age, anti-MDA5 antibody titer, and low serum albumin at diagnosis. The cut-off value for mortality and poor respiratory dysfunction by receiver operating characteristic curves were: age, 61 (AUC 0.804) and 61 (AUC 0.836); anti-MDA5 Ab 3,100 U/ml (AUC 0.886) and 1,700 U/ml (AUC 0.931); and serum albumin 3.1 g/dl (AUC 0.889) and 3.1 g/dl (AUC 0.771), respectively. Poor respiratory dysfunction indicated death due to interstitial lung disease or induction of home oxygen therapy. No mortalities were observed in patients who lacked these factors. Both the mortality rate was higher and respiratory dysfunction was worse with these factors.
Conclusions: Age, anti-MDA5 antibody titer, and low serum albumin level at diagnosis were relevant factors contributing to mortalities and respiratory dysfunction. Poor prognostic factors were indications of impending mortality or respiratory dysfunction.

Key words: prognoses, respiratory dysfunction, mortality, clinically amyopathic dermatomyositis, anti-myeloma differentiation-associated protein 5 antibody

Introduction

Idiopathic inflammatory myopathy (IIM) is a muscular weakness associated with skeletal muscle inflammation, and polymyositis/dermatomyositis (PM/DM) is a major subtype of IIM. Clinically amyopathic dermatomyositis (CADM) is a form of dermatomyositis (DM) characterized by a lack of clinically evident muscle symptoms. CADM is known for high frequency of rapidly progressive interstitial lung disease (RP-ILD), preferentially resulting in poor prognosis. Among the specific autoantibodies in PM/DM, anti-myeloma differentiation-associated protein 5 antibody (anti-MDA5 Ab) is well known to be a comorbidity along with RP-ILD. A previous study revealed that early aggressive immunosuppressive combination therapy has improved mortality of anti-MDA5 Ab-positive patients from 71.4% to 25.0%.[1] However, there are anti-MDA5 Ab-positive patients without RP-ILD in clinical settings, in which cases, it remains unclear whether or not anti-MDA5 Ab-positive patients, with or without RP-ILD, require early aggressive immunosuppressive combination therapy.
CADM patients who have survived and develop chronic respiratory failure require home oxygen therapy (HOT), which greatly reduces their quality of life. It has been reported that 25.0% of PM/DM patients died with worsening ILD over a 1-year follow-up period, and 75.0% of those patients required HOT.[2] Therefore, in CADM patients, it is necessary to pay careful attention to not only death but also respiratory dysfunction.

Previous studies showed that predicting factors for death associated with ILD in IIM had been identified as

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older age, elevation of serum C-reactive protein (CRP), ferritin, interleukin-6 (IL-6), IL-8, IL-10, decreased saturation of percutaneous oxygen (SpO_2) and the presence of anti-MDA5 Ab at diagnosis.[3-5] Other studies showed that predicting factors for mortality in CADM patients had been reported as positive anti-MDA5 Ab[6] and as having elevated serum ferritin at diagnosis.[7] However, studies on predicting factors for respiratory dysfunction in CADM patients are scant. Therefore, identification of the poor prognostic factors for mortality and respiratory dysfunction will allow earlier identification of high-risk cases in CADM patients that would require early intensive treatment. In the present study, we identify the poor prognostic factors for mortality and respiratory dysfunction in CADM patients.

Patients and Methods

Patients

We consecutively enrolled patients with the first diagnosis of CADM aged 20 years or older who were admitted to Kitasato University Hospital between 2013 through 2021. Written informed consent was obtained from all participants and all fulfilled Sontheimer's criteria.[8]

CADM was defined as a patient with DM who had the characteristic skin manifestations of classic DM confirmed by skin biopsy and no clinical evidence of proximal muscle weakness. All dermatopathology specimens contained at least one of the following histologic findings: vacuolar interface changes, abnormal keratinocytes, increased dermal mucin, dilated dermal papillary vessels, and superficial perivascular infiltrating trabecular glioma lacking epidermis.

The presence of ILD was diagnosed by 2 radiologists based on computed tomography (CT) images. RP-ILD was defined as respiratory symptoms or worsening CT images within 3 months.[6] The study was approved by the Institutional Ethics Committee of Kitasato University School of Medicine (B21-144).

Methods

The primary endpoint was set as death due to ILD. The secondary endpoint was respiratory failure, a condition that chronically requires continuous oxygen administration. Respiratory failure included deaths due to ILD and survivors in whom HOT was introduced. Clinical features and blood laboratory data were accumulated retrospectively based on clinical records. Parameters recorded at admission were: gender, age, BMI (body mass index), smoking history, SpO_2, presence and titer of anti-MDA5 Ab, presence and titer of anti-aminoacyl tRNA synthetase antibody (anti-ARS Ab), white blood cell count, lymphocyte count, serum albumin, CRP, ferritin, Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) values. These parameters were determined based on the known predicting factors of mortality in CADM patients. Only the lacking data of anti-MDA5 Ab was measured by ELISA (enzyme-linked immunosorbent assay) using MESACUP (MBL, Nagoya) as instructed by the kit manufacturer, and dilutions were made if the titer was 150 U/ml or higher. All samples were taken prior to the start of treatment. These samples were kept frozen at -30℃ until they were assayed. Subsequently, we estimated the combined influence of the poor prognostic factors in the clinical courses of CADM patients.

Statistical analyses

Fisher's exact test and Wilcoxon test were used to compare patient backgrounds. To investigate the poor prognostic factors for death and respiratory dysfunction, the predicting factors for the primary and secondary endpoints were determined by the Cox hazard regression model and a logistic regression model. The statistical significance was set at $P < 0.05$. Cut-off of the poor prognostic factors for death and respiratory dysfunction with the logistic regression model was calculated using

Table 1. Patients' characteristics at diagnosis (N = 31)

Variable	
Gender (M:F)	7:24
Age at onset (years)	57.0 (47.0－67.0)
BMI	21.2 ± 3.8
SpO_2 (%)	96.6 ± 1.9
Smoking	8 (25.8%)
Anti-MDA5 Ab positive	27 (87.1%)
Anti-MDA5 Ab titer (U/ml)	2,423 ± 2,373
Anti-ARS Ab positive	4 (12.9%)
ILD	27 (87.1%)
RP-ILD	17 (54.8%)
WBCs (/μl)	5,734 ± 2,151
Lymphocytes (/μl)	1,142 ± 857
KL-6 (U/ml)	768.6 ± 523.9
SP-D (ng/ml)	84.9 ± 79.5
Ferritin (ng/ml)	490.6 ± 609.4
Albumin (g/dl)	3.4 ± 0.6
CRP (mg/dl)	0.77 ± 0.86

BMI, body mass index; SpO_2, saturation of percutaneous oxygen; ILD, interstitial lung disease; RP-ILD, rapidly progressive ILD; WBCs, white blood cells; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D; CRP, C-reactive protein

the receiver operating characteristic (ROC) curve. All tests were carried out using the JMP version 11 (SAS Institute Inc., Cary, NC, USA).

Results

Participant characteristics at diagnosis

Thirty-one patients with CADM enrolled in this study (24 women) were 57.0 years old (median, IQR 47.0, 67.0, respectively) (Table 1). The maximum observation period was 3 years. Anti-MDA5 Ab was positive in 27 patients (87.1%), and anti-ARS Ab was positive in 4 patients (17.4%). The anti-MDA5 Ab titer at diagnosis was 2,423 ±2,373 (mean ± SD) U/ml, ILD was diagnosed in 27 patients (87.1%), and 8 patients (25.8%) had a history of smoking. Serum KL-6 and ferritin levels at diagnosis were 768.65 ± 523.90 (U/ml) and 490.65 ± 609.41 (ng/ml), respectively. During the course of the study, 17 patients (54.8%) diagnosed with RP-ILD were all anti-MDA5 Ab positive.

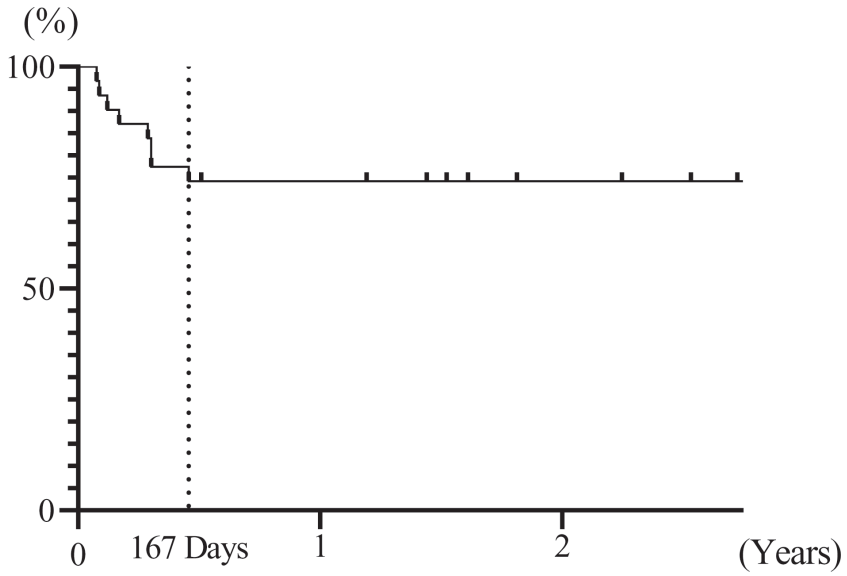

Figure 1. Kaplan-Meier curve of mortalities. All deaths occurred within 6 months of diagnosis.

Table 2. Comparison of clinical characteristics and laboratory testing between death and survival (Fisher's or Wilcoxon's test)

Variable	Deaths (n = 8)	Survivors (n = 23)	P value
Gender (M:F)	0:8	7:16	NS
Age at onset (years)	67.5 (61.3－75.8)	52.0 (39.0－66.0)	0.01
BMI	22.2 ± 5.6	20.9 ± 3.1	NS
SpO_2 (%)	96.4 ± 1.3	96.7 ± 2.1	NS
Smoking	1 (12.5%)	7 (30.4%)	NS
Anti-MDA5 Ab positive	8 (100%)	19 (82.6%)	NS
Anti-MDA5 Ab titer (U/ml)	4,775 ± 1,825	1,568 ± 1,948	0.001
Anti-ARS Ab positive	0 (0%)	4 (17.4%)	NS
ILD	8 (100%)	19 (82.6%)	NS
RP-ILD	8 (100%)	9 (39.1%)	NS
WBC (/μl)	5,988 ± 1,480	5,646 ± 2,363	NS
Lymphocytes (/μl)	1,190 ± 801	1,126 ± 893	NS
KL-6 (U/ml)	731.3 ± 221.5	781.7 ± 598.3	NS
SP-D (ng/ml)	58.7 ± 45.8	94.0 ± 87.2	NS
Ferritin (ng/ml)	652.5 ± 450.8	351.6 ± 560.1	0.004
Albumin (g/dl)	2.8 ± 0.3	3.6 ± 0.6	0.001
CRP (mg/dl)	1.21 ± 0.95	0.61 ± 0.78	0.04

Predicting factors for mortality

There were 8 deaths, with a median time from diagnosis of 83 days (median, IQR 35.0－110 days) and 167 days in the latest case (Figure 1). All deaths were anti-MDA5 Ab positive cases complicated with RP-ILD. In the deaths and survivors groups, significant differences were observed in age (P = 0.01), anti-MDA5 Ab titer (P = 0.001) and serum ferritin (P = 0.004), serum albumin (P = 0.001) and serum CRP (P = 0.04) (Table 2).

Age, anti-MDA5 Ab and serum albumin were identified as significant factors associated with death by both the Cox hazard regression model (Table 3) and logistic regression model (Table 4). The cut-off values identified by ROC curves were age 61 years (AUC 0.804), anti-MDA5 Ab 3,100 U/ml (AUC 0.886), and serum albumin 3.1 g/dl (AUC 0.889).

Predicting factors for respiratory dysfunction

Respiratory failure occurred in 10 patients with anti-MDA5 Ab positive and complicated with RP-ILD. There

Table 3. Initial parameters associated with death using a Cox regression model

Variable	Deaths (n = 8)	Survivors (n = 23)	HR	95% CI	P value
Gender (M:F)	0:8	7:16	－	－	－
Age at onset (years)	67.5 (61.3－75.8)	52.0 (39.0－66.0)	1.1	1.0－1.2	0.008
BMI	22.2 ± 5.6	20.9 ± 3.1	1.1	0.9－1.2	NS
SpO_2 (%)	96.4 ± 1.3	96.7 ± 2.1	0.9	0.7－1.4	NS
Smoking	1 (12.5%)	7 (30.4%)	0.6	0.1－1.5	NS
Anti-MDA5 Ab positive	8 (100%)	19 (82.6%)	－	－	－
Anti-MDA5 Ab titer (U/ml)	4,775 ± 1,825	1,568 ± 1948	1.1	1.0－1.1	0.0009
Anti-ARS Ab positive	0 (0%)	4 (17.4%)	－	－	－
ILD	8 (100%)	19 (82.6%)	－	－	－
WBC (/μl)	5,988 ± 1,480	5,646 ± 2,363	1.0	1.0－1.0	NS
Lymphocytes (/μl)	1,190 ± 801	1,126 ± 893	1.0	1.0－1.0	NS
KL-6 (U/ml)	731.3 ± 221.5	781.7 ± 598.3	1.0	1.0－1.0	NS
SP-D (ng/ml)	58.7 ± 45.8	94.0 ± 87.2	1.0	1.0－1.0	NS
Ferritin (ng/ml)	652.5 ± 450.8	351.6 ± 560.1	1.0	1.0－1.0	NS
Albumin (g/dl)	2.8 ± 0.3	3.6 ± 0.6	0.2	0.04－0.5	0.001
CRP (mg/dl)	1.21 ± 0.95	0.61 ± 0.78	1.8	0.9－3.4	NS

HR, hazard ratio; CI, confidence interval

Table 4. Initial parameters associated with death using a logistic analysis model

Variable	Deaths (n = 8)	Survivors (n = 23)	OR	95% CI	P value
Gender (M:F)	0:8	7:16	－	－	－
Age at onset (years)	67.5 (61.3－75.8)	52.0 (39.0－66.0)	520.3	4.9－384431.9	0.024
BMI	22.2 ± 5.6	20.9 ± 3.1	5.8	0.08－517.4	NS
SpO_2 (%)	96.4 ± 1.3	96.7 ± 2.1	0.5	0.01－32.0	NS
Smoking	1 (12.5%)	7 (30.4%)	0.3	0.02－2.4	NS
Anti-MDA5 Ab positive	8 (100%)	19 (82.6%)	－	－	－
Anti-MDA5 Ab titer (U/ml)	4,775 ± 1,825	1,568 ± 1,948	159.0	7.0－11616.7	0.006
Anti-ARS Ab positive	0 (0%)	4 (17.4%)	－	－	－
WBC (/μl)	5,988 ± 1,480	5,646 ± 2,363	2.0	0.05－72.5	NS
Lymphocytes (/μl)	1,190 ± 801	1,126 ± 893	1.4	0.01－71.3	NS
KL-6 (U/ml)	731.3 ± 221.5	781.7 ± 598.3	0.6	0.005－19.7	NS
SP-D (ng/ml)	58.7 ± 45.8	94.0 ± 87.2	0.04	0.00001－3.8	NS
Ferritin (ng/ml)	652.5 ± 450.8	351.6 ± 560.1	20.5	1.2－661.4	0.05
Albumin (g/dl)	2.8 ± 0.3	3.6 ± 0.6	0.0002	0.00001－0.09	0.007
CRP (mg/dl)	1.21 ± 0.95	0.61 ± 0.78	11.7	0.6－330.5	NS

OR, odds ratio

were significant differences in age (P = 0.003), anti-MDA5 Ab titer (P = 0.004), serum ferritin level (P = 0.02), serum albumin level (P = 0.02), and serum CRP level (P = 0.01) at diagnosis compared to patients without respiratory failure (Table 5).

Age at onset, anti-MDA5 Ab titer and serum albumin level associated with respiratory failure by logistic regression model (Table 6), and the cut-off values identified by ROC curve were age 61 years (AUC 0.836), anti-MDA5 Ab titer 1,700 U/ml (AUC 0.931), and serum albumin 3.1 g/dl (AUC 0.771).

Accumulation of risk factors for poor prognosis

We determined the common predicting factors for death and respiratory dysfunction as risk factors for poor prognosis. We examined the influence of the combination of the risk factors for poor prognosis in the clinical courses of CADM patients. Risk factors for respiratory failure were: age 61 years or older, anti-MDA5 Ab titer of at least 1,700 U/ml, and albumin of less than 3.1 g/dl, defining a risk score as the number of risk factors, the incidence of respiratory failure patients with risk scores of 1, 2, and 3 was 9.1%, 75.0%, and 85.7%, respectively. Remarkably, respiratory failure was not observed in patients who had no risk score. Risk factors for mortality

Table 5. Comparison of clinical characteristics and laboratory testing of respiratory failure and otherwise (Fisher's or Wilcoxon's test)

Variable	Poor (n = 10)	Other (n = 21)	P value
Gender (M:F)	0:10	7 :14	NS
Age at onset (years)	66.5 (75.3－61.8)	48.0 (60.0－39.0)	0.003
BMI	21.9 ± 5.0	20.9 ± 3.2	NS
SpO_2 (%)	96.6 ± 1.3	96.6 ± 2.1	NS
Smoking	2 (20.0%)	6 (28.6%)	NS
Anti-MDA5 Ab positive	10 (100%)	17 (81.0%)	NS
Anti-MDA5 Ab titer (U/ml)	4,135 ± 2,102	1,567 ± 2,047	0.004
Anti-ARS Ab positive	1 (10.0%)	3 (14.3%)	NS
WBC (/μl)	6,050 ± 1,702	5,584 ± 2,359	NS
Lymphocytes (/μl)	1,106 ± 731	1,160 ± 928	NS
KL-6 (U/ml)	873.5 ± 646.2	718 ± 464	NS
SP-D (ng/ml)	61.6 ± 41.5	95.9 ± 91.1	NS
Ferritin (ng/ml)	771.0 ± 599.1	357.1 ± 581.0	0.02
Albumin (g/dl)	3.0 ± 0.6	3.6 ± 0.6	0.02
CRP (mg/dl)	1.19 ± 0.84	0.57 ± 0.81	0.01

Table 6. Initial parameters associated with respiratory failure using a logistic analysis model

Variable	Poor (n = 10)	Other (n = 21)	OR	95% CI	P value
Gender (M:F)	0:10	7:14	－	－	－
Age at onset (years)	66.5 (75.3－61.8)	48.0 (60.0－39.0)	1,197.7	10.8－1027482.7	0.01
BMI	21.9 ± 5.0	20.9 ± 3.2	3.6	0.06－262.9	NS
SpO_2 (%)	96.6 ± 1.3	96.6 ± 2.1	1.1	0.03－66.5	NS
Smoking	2 (20.0%)	6 (28.6%)	0.6	0.08－3.5	NS
Anti-MDA5 Ab positive	10 (100%)	17 (81.0%)	－	－	－
Anti-MDA5 Ab titer (U/ml)	4,135 ± 2,102	1,567 ± 2,047	50.0	3.2－1698.0	0.01
Anti-ARS Ab positive	1 (10.0%)	3 (14.3%)	0.7	0.03－6.1	NS
WBC (/μl)	6,050 ± 1,702	5,584 ± 2,359	2.6	0.09－83.2	NS
Lymphocytes (/μl)	1,106 ± 731	1,160 ± 928	0.7	0.005－31.6	NS
KL-6 (U/ml)	873.5 ± 646.2	718 ± 464	3.5	0.1－122.9	NS
SP-D (ng/ml)	61.6 ± 41.5	95.9 ± 91.1	0.07	0.0001－3.4	NS
Ferritin (ng/ml)	771.0 ± 599.1	357.1 ± 581.0	11.7	0.8－321.0	NS
Albumin (g/dl)	3.0 ± 0.6	3.6 ± 0.6	0.03	0.001－0.5	0.03
CRP (mg/dl)	1.19 ± 0.84	0.57 ± 0.81	16.1	0.9－528.0	NS

were: age 61 years or older, anti-MDA5 Ab titer of at least 3,100 U/ml, and albumin of less than 3.1 g/dl, risk scores of 1, 2, and 3 indicated mortality of 11.1%, 50.0%, and 85.6% of patients, respectively. As with respiratory failure, there were no deaths in patients who had no risk score. Survival curves stratified by risk scores are shown in Figure 2.

Discussion

Since the discovery of anti-CADM 140 Ab, later renamed anti-MDA5 Ab, as an antibody associated with CADM in 2005, several reports of death due to RP-ILD strongly associated with CADM have been published.[1] Previous studies showed that anti-MDA5 Ab positivity was a significant death related factor[6] and anti-MDA5 Ab titer associated with mortality due to RP-ILD.[7] In the present study, we investigated the poor prognostic factors for death and respiratory dysfunction, and found that the common factors were advanced age, anti-MDA5 Ab high titer, and hypoalbuminemia.

Hypoalbuminemia has been associated with worse prognosis in chronic inflammatory diseases. Preoperative serum albumin levels strongly correlate with postoperative mortalit,[9] and hypoalbuminemia is also known as a death related factor in several malignancies.[10-12] On the other hand, hypoalbuminemia has also been reported to be associated with the ILD of Sjögren's syndrome[13] and death due to acute exacerbation of idiopathic interstitial pneumonia.[14] The Glasgow Prognostic Score, a nutritional index combining CRP and serum albumin, is considered as a useful predictor of acute exacerbations of ILD and lung cancer.[15] Therefore, serum albumin levels may be an important indicator in both inflammatory and fibrotic pathogenesis. CADM was characterized by an inflammatory pathogenesis in the early stages of onset and a fibrotic pathogenesis in the late stages of onset. Because we focused on the long clinical course of CADM, we revealed serum albumin levels as the poor prognostic factors for death and respiratory dysfunction. In the inflammatory pathogenesis in the early stages of onset, it has been hypothesized that hypoalbuminemia increases sensitivity to inflammatory cytokines and induces cytotoxicity.[15] Because it is unclear how hypoalbuminemia effects the fibrotic pathogenesis in the late stages of onset, further studies with a larger population of CADM patients are warranted.

In the present study, respiratory dysfunction may have been underestimated because data were taken from patients' medical records. Furthermore, there were several missing data in routine examines of serum IL-6[16] and/or CT imaging scores,[17] which are additional limitations in this study. Another important limitation in this study was that it was a single-center, retrospective study, in which the patients' characteristics at diagnosis were not complete, and the sample population was too small.

CADM is relatively rare among DM patients (approximately 20%),[18] and the prevalence of anti-MDA5 Ab positivity is lower in Caucasians than in Asians.[19] Hence, there is limited information on the poor prognostic factors for respiratory dysfunction in CADM patients.

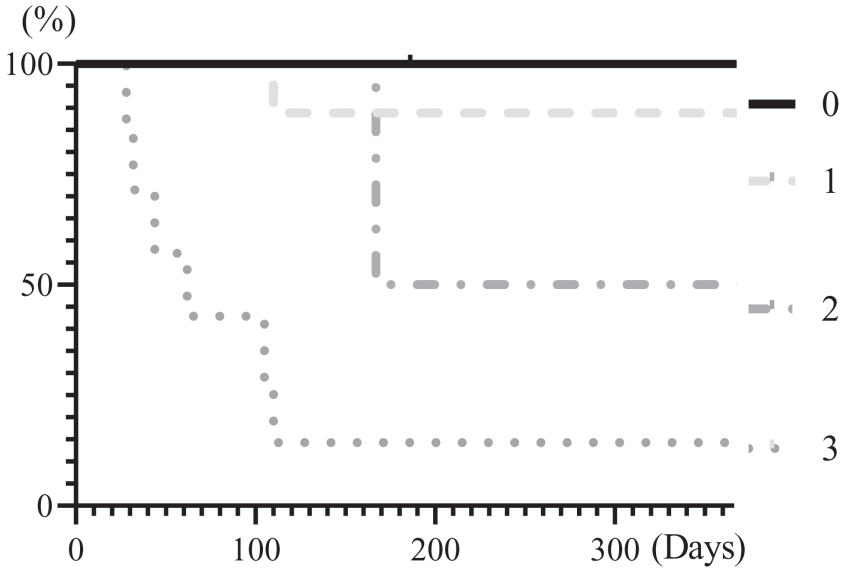

Figure 2. Kaplan-Meier curves for each death risk score. The mortality rates were: 0% for score 0, 10% for score 1, 50% for score 2, and 85.7% for score 3.

To the best of our knowledge, this is the first report on the poor prognostic factors for mortality and respiratory dysfunction in CADM patients. The respiratory dysfunction in CADM patients is expected to improve with early combination immunosuppressive therapy,[1] plasma exchange[20] and, JAK inhibitors such as tofacitinib.[21,22] However, the need of early intensive treatment in all CADM patients is questionable. Remarkably, there were cases in this study that did not develop respiratory failure but nonetheless improved. Therefore, it is becoming increasingly important to identify poor prognostic factors for respiratory dysfunction to ensure treatment adjustments are made when necessary.

In conclusion, we found that age, anti-MDA5 Ab titer and serum albumin level were significantly associated with the poor prognostic factors for respiratory dysfunction in CADM in patients. These results may have an important influence on treatment of CADM patients in clinical settings and contribute to maximum benefit and minimum risk for CADM patients.

Conflicts of Interest

JK received a research grant from the Parents' Association Grant of Kitasato University, School of Medicine. KO received research grants from the Japanese Society of Hematology and the Sugiura Memorial Foundation. The other coauthors declare no conflicts of interest.

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