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ORIGINAL ARTICLE

Mortality of Chinese patients with polymyositis and dermatomyositis

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Abstract

Objective To investigate the mortality and the causes of death in Chinese patients with polymyositis (PM) and dermatomyositis (DM).

Methods The clinical data of all consecutive adult PM/DM patients in Rheumatology and clinical immunology department of Peking University First Hospital from January 2007 to Apr2016 were collected. The primary causes of death were identified, the standardized mortality ratio (SMR) and years of life lost (YLL) were calculated based on the National Bureau of Statistics of China for the general population, the survival in the first decade was performed using Kaplan-Meier analysis, and the predictors of mortality were evaluated by multivariable cox regression.

Results A total of 85 PM and226 DM cases were included and 68 patients died. Infection (52.3%) was the leading cause of death. The overall age and sex adjusted SMR was 6.0(95%CI 3.5–8.5) for PM, and 9.0(95%CI 6.8–11.2) for DM. The YLL of women and men were 12.2 and 18.3 years respectively for PM, and 37.5 and 28.4 years respectively for DM. The 10-year survival of patients with ILD, malignancy or infection was significantly worse than those without, respectively. The independent predictors of mortality for PM/DM patients were age at disease onset, malignancy and infection.

Conclusions Mortality of PM/DM patients in China is substantial, especially in females, and those with ILD, malignancy or infection. Infection was the leading cause of death. Patients with older age at onset, infection, ILD, and malignancy need to be paid more attention.

Key Points

- *This is the first comprehensive report about the mortality situation with a large population in PM/DM patients in China including SMR, YLL, and cause of death, Kaplan-Meier survival analysis and Cox regression analysis for mortality risk factors.*
- *The specific SMRs for PM/DM patients with malignancy and interstitial lung disease were also reported in this study. To our knowledge, only two studies worldwide reported SMRs in PM/DM patients and no figure about YLL was reported so far.*
- *Overall, the mortality figures in this study were higher than those from the western countries, and the leading cause of death was different from the western countries.*

Keywords Dermatomyositis · Mortality · Polymyositis · Predictors for outcomes

Introduction

Polymyositis (PM) and dermatomyositis (DM) are two of the most common types of inflammatory muscle disorders, with internal organs such as lung and heart involvement in many cases. In addition to the burden from disease itself, the close association between PM/DM and malignancy also plays an important role in the prognosis of PM/DM [1]. Some studies reported that the 10-year survival rates of PM/DM ranged from 42% to 85% [2–9] and the mortality rates of 10-year were reported to be as high as 42% to 74% [2–5]. Nevertheless, the reports on mortality in Chinese patients with PM/DM are very limited, and there is none from mainland China so far. In order to understand the mortality situation in patients with PM/DM in mainland China and a series of relevant issues, we undertook this research with the purpose of estimating the mortality rate, and determining the causes and the risk factors of death.

Xinlei Yang and Yanjie Hao contributed equally to this work.

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Materials and methods

Study population

We reviewed all the medical records of PM/DM patients who visited Peking University First Hospital. The hospital involved in the present study is a tertiary and referral medical center, and the patients who visit this center come from nationwide including urban and rural areas, therefore the data have certain capability to reflect the characteristics of the whole nation. A retrospective study was performed in the patients with PM/DM from January 2007 to Apr 2016.The inclusion criteria were adults (≥18 years old) with definite diagnosis of PM/DM which met the classification criteria proposed by Bohan and Peter in 1975 [10, 11], and had at least one follow-up visit in our center. Patients with immune-mediated necrotizing myopathy (IMNM) were included in PM group, and IMNM was diagnosed according to the pathological results of muscle biopsy. Patients with amyopathic DM (ADM) were included in DM group, and ADM was defined as typical DM rash, lack of muscle weakness and normal creatine kinase (CK) [12, 13]. Patients with inclusion body myositis as well as myositis associated or overlapped with other connective tissue diseases (CTD-overlap myositis) were excluded. Inclusion body myositis was diagnosed according to muscle biopsy, and CTD-overlap myositis was defined as PM/DM coexisting with a CTD that met relevant diagnostic criteria [2].Demographic, clinical characteristics and laboratory parameters were ascertained from the medical records. The ethics approval was obtained from the human research ethics committees of Peking University First Hospital (approval number: 2018038).

Definitions

The diagnosis of interstitial lung disease (ILD) was based on HRCT findings including reticular, irregular linear, ground-glass opacities, consolidation, traction bronchiectasis, and honeycombing [2, 14, 15]. Cardiac involvement was defined as the occurrence of pericarditis, myocarditis, arrhythmia or sinus tachycardia occurring due to the myositis disease process [2, 16]. The diagnosis of respiratory involvement was referred to the article by Gosselink et al. [17]: 1) the patient's report of difficulty in clearing pulmonary secretions; 2) the patient's report of a weakened cough; 3) the examiner's observation of the patient's cough; 4) the ability to count on a single exhalation; and 5) eliminating the disease that causes the above situation.

Patients were defined as having infectious complications based on clinical features, positive etiological evidence and response to anti-infectious treatment. A major infection was defined as one that necessitated the use of i.v. and/or prolonged course of anti-microbial agents of duration >1 week [18]. Upper respiratory infection and lower urinary tract infection were not included.

Mortality data

Survival status was ascertained up until Jul 31, 2016 based on the records in the databases and telephone tracing of patients in whom no data had been entered for ≥12 months in the database. The final status of loss to follow-up was defined as one where no data had been entered for ≥12 months with a failure to contact the patient despite at least two attempts.

Calculation of standardized mortality ratio (SMR)

The standardized mortality ratio (SMR) was used to compare the mortality of subjects with PM/DM relative to that of the general population of China. SMR and its 95% confidence interval (CI) were calculated as follows [19–21]:

$$SMR = \frac{O}{E}$$

$$95\%CI = \left(SMR - 1.96 \times \frac{\sqrt{O}}{E}, SMR + 1.96 \times \frac{\sqrt{O}}{E}\right)$$

where O is the observed number of deaths in the study population and E is the expected number of deaths. The expected number of deaths is the product of the total number of person-years contributed by the study population and the mortality rate of the general population. The age- and sex-adjusted SMRs were calculated similarly; the expected number of deaths was stratified by 10-year age groups and sex. The mortality rates of the general population were obtained from the data of the 2010 national population census from National Bureau of Statistics of China. The nationwide census is carried out every 10 years in China and the one was in 2009/10. Therefore, the most recent available mortality data of the general population in China at the time of the present analysis was from Nov 1st, 2009 to Oct 31th, 2010. We calculated SMRs for our cohort from Jun 2007 to Jun 2016. In relation to losses to follow up, sensitivity analyses were performed to re-calculate SMR assuming that all of these patients were (i) alive and (ii) dead at the end of the study.

The specific SMRs of patients with ILD and malignancy were also calculated.

Calculation of life expectancy (LE) and years of life lost (YLL)

LE for the study population as well as the general population was calculated according to sex by a period abridged life table as described by Chiang and Newell [21–23] using 5-year age

intervals up to the oldest age interval of 85+ years. The calculations used the same data as for SMR calculations above. YLL was calculated as follows:

$$YLL = LE\_g$$

Where LE_g is life expectancy at the time of birth in the general population and LE_s is life expectancy at the time of birth in the study population.

Causes of death

The medical records of the patients who died in our hospital were examined to ascertain the causes of death. For patients who died outside our hospital, the causes of death were determined via tracing the medical records of the hospital or the emergency center where the patients died. Each PM/DM organ involvement which contributed to the death was defined using the definitions as presented in the 'definitions' part.

Statistical analysis

Data are presented as mean ± standard deviation (SD) for continuous variables, median (interquartile range) for abnormally distributed continuous variables and numbers (percentages or proportions) for categorical variables. Baseline characteristics were compared between subjects who were alive and those who had died. Normally distributed continuous variables were compared using the student t-test with unequal variances, whereas abnormally distributed continuous variables were compared using Kruskall-Wallis and Mann-Whitney U tests. The differences in frequency were determined using chi-square and Fisher's exact tests.

Survival analysis in the first decade was performed using the Kaplan-Meier method with comparisons performed using the log-rank test. The primary endpoint was all-cause death or data censoring. The follow-up period ended on Jul 31, 2016. The disease duration was defined as the time from disease onset until death or last follow-up.

Univariable and multivariable Cox proportional hazards models were used to determine the variables associated with mortality. Age, gender, disease duration at recruitment, clinical manifestations, organ involvements, serum CK, anti-Jo-1 antibody, pulmonary function test parameters, complications and comorbidities were included in the univariable Cox hazards model. Variables with significance in the univariable analysis were then included in the multivariable Cox hazards regression analysis wherein we ensured the proportionality of hazard assumption was valid.

A two-tailed p value ≤0.05 was used to indicate statistically significant differences. All statistical analyses were performed using STATA 12.0 (Statacorp, College Station, TX, USA).

Results

Characteristics of subjects

There were totally 504 adult patients with PM/DM who fulfilled the Bohan and Peter criteria in Peking University First Hospital between Jan 2007 and Apr 2016. After excluding patients with CTD-overlap myositis and who did not have any follow-up visit, 311 (85 PM and 226 DM) (Fig. 1) patients were eventually included in the study. The 85 PM comprised 30 patients with IMNM. The 226 DM comprised 12 patients with ADM. The mean age at disease onset was 48.1 ± 17.1 years for PM and 49.9 ± 14.8 years for DM. The median (interquartile range) follow-up duration was 3.6(1.5–5.4) years for PM and 2.5 (0.6–4.7) years for DM. In terms of organ involvement, 112(36.0%) subjects were identified with ILD (26 PM and 86 DM), 26(8.4%) with respiratory muscle involvement (3 PM and 23 DM) and 8(2.6%) with cardiac involvement (3 PM and 5 DM). Among the 311 PM/DM patients, we observed 81(26.0%) patients (17 PM and 64DM) complicated with infection and 42 (13.5%) patients (6 PM and 36 DM) with malignancy. Malignancy was predominantly observed in DM patients (15.9% vs. 7.1%; P = 0.030), and ILD was also predominantly observed in DM patients (54.1% vs. 32.5%; P = 0.002).There was no difference between patients with PM and those with DM in terms of the prevalence of infections. Among the 311 PM/DM patients, 81 (26.0%) developed major infections with a total of 104 episodes including 60 (74.1%) patients with one infectious episode and 21 (25.9%) patients with two or more episodes. In terms of pathogens, Candidiasis (20/104, 19.2%), Klebsiella (15/104, 14.4%), *Staphylococcus aureus* (14/104, 13.5%), and pneumocystis jiroveci pneumonia (8/104, 7.7%) were the top four types (Supplementary Table 1). The comparison between PM and DM in terms of the demographics, baseline clinical and laboratory characteristics, organ involvements, pulmonary function test and major comorbidities during the whole disease course were summarized in Table 1.

There were 13 patients lost to follow-up by the end of Jul 312,016, and among the rest 298patients who were successfully traced, 68 patients died (13 PM and 55 DM). There was no significant difference in the death rate between PM and DM (15.3% vs. 24.3%, p = 0.086), but the age at death was significantly older for the PM patients than the DM patients (69.4 ± 12.5 vs.59.2 ± 14.4 years; P = 0.022). In the PM cohort, compared with the subjects who were alive at the end of the follow-up, those who died were significantly older at disease onset (47.8 ± 16.1 vs. 64.9 ± 12.2, p < 0.001).In the DM cohort, the same trend was also noticed (47.9 ± 14.2 vs56.1 ± 15.2, p < 0.001).In both PM and DM cohort, the subjects who died were more likely to have infection and malignancy than those who were alive. Meanwhile, in the DM cohort, those who died were more likely to have respiratory muscle

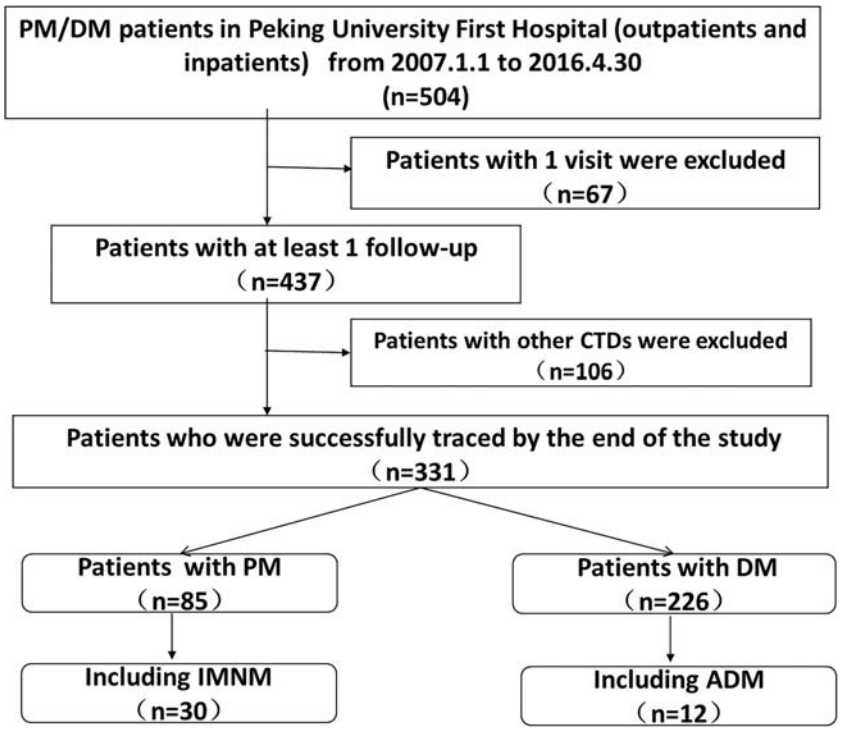

Fig. 1 Flow chart of the included.PM: polymyositis; DM:dermatomyositis; CTDs: connective tissue diseases

involvement and ischemic heart disease than those who were alive (Supplementary Table 2).

SMR, LE and YLL

SMR

The overall age and sex adjusted SMR for patients with DM was significantly higher than those with PM (9.0 (95%CI 6.8–11.2) vs. 6.0 (95%CI 3.5–8.5)). In DM patients, the age-adjusted SMR for females was higher than that of males (12.0 (8.1–15.9) vs. 6.0 (3.2–8.7)). In the subgroup of DM patients with ILD, the age-adjusted SMR for females was higher than that of males (15.4(8.5–22.3) vs. 5.1(1.0–9.2)), and in the subgroup of DM patients with infection, the age-adjusted SMR for females was also higher than that of males (38.5(22.8–54.2) vs.15.0 (6.1–23.8)). However, in the subgroup of DM patients with malignancy, males had much higher age-adjusted SMR than females (48.7(12.6–84.7) vs. 8.2(2.1–14.3)). In PM patients, the age-adjusted SMR for males was lower than that of females (5.5 (0.7–10.2) vs.6.2 (2.8–9.6)). Due to the small number of death in the subgroup of PM with ILD and malignancy, the specific SMRs for both the subgroups were not calculated (Table 2).

SMR sensitivity analyses

In SMR sensitivity analyses, (i) assuming all loss to follow-up were alive, the overall age and sex adjusted SMRs for patients with DM and PM were 6.6(5.1–8.1) and 5.7(3.2–8.1), respectively; (ii) assuming all loss to follow-up were dead, the overall age and sex adjusted SMR for patients with DM and PM were 11.0(8.5–13.4) and 6.6(3.9–9.3), respectively (Supplementary Table 3).

LE and YLL

The LE at birth of Chinese general population was 80.8 years for women and 75.8 years for men according to the data of the 2010 national population census from National Bureau of Statistics of China. The LE of the PM patients was 62.5 years for women, and 63.6 years for men. The LE of the DM patients was 43.3 years for women, and 47.4 years for men. Therefore, the YLLs were 18.3 years and 12.2 years for females and males respectively in the PM cohort, and 37.5 years and 28.4 years for females and males respectively in the DM cohort (Table 2).

Survival analysis

The overall survival in the first decade of disease in the DM cohort was lower than the PM cohort, but there was no significantly statistical difference (81.5%, 76.6% and 71.7% vs. 94.6%, 87.5% and 84.8%, at 1, 5 and 10 years respectively, $p = 0.070$) (Fig. 2). After combining PM and DM patients, the Kaplan-Meier analysis revealed a significantly lower survival in the patients with respiratory muscle involvement than those without respiratory muscle involvement (65.2%, 52.2% and 50.0% vs.90.2%, 84.8% and 77.2%, at 1, 5 and 10 years

Table 1 The characteristics of patients with PM and DM

Characteristics	Polymyositis $n = 85$	Dermatomyositis $n = 226$	*P* value
Female	53(62.4)	163(72.1)	0.095
Age at disease onset[a], years	50.4 ± 16.7	48.1 ± 17.1	0.776
Age at recruitment[b], years	52.6 ± 16.6	51.8 ± 14.6	0.688
Disease duration at recruitment[c], years	0.5(0.2–2.4)	0.4(0.2–1.0)	0.489
Follow-up duration[d], years	3.6(1.5–5.4)	2.5(0.6–4.7)	0.180
Number of deaths	13(15.3)	55(24.3)	0.086
Age at death, years	69.4 ± 12.5	59.2 ± 14.4	0.022
Disease duration at death[e], years	2.7(1.1–8.5)	0.5(0.2–2.0)	0.000
Baseline clinical manifestations			
Fever	17(20.0)	61(27.0)	0.205
Gottron's papule	–	113(50.0)	–
Heliotrope rash	–	199(88.1)	–
Mechanic's hand	–	47(20.8)	–
Raynaud's phenomenon	2(2.4)	5(2.2)	0.941
Arthralgia	7(8.2)	57(25.2)	0.001
Organ involvements[f]			
Cardiac involvement	3(3.5)	5(2.2)	0.801
Respiratory muscle involvement	3(3.5)	23(10.2)	0.059
ILD	26(32.5)/80[g]	86(54.1)/159[g]	0.002
Baseline Laboratory examinations			
LDH, IU/L	345.0(258.5–535.5)	297.0(215.5–436.8)	0.086
HBDH, IU/L	302.0(223.3–485.3)	256.0(190.0–375.0)	0.826
CK, IU/L	1162.0(407.3–2973.0)	127.5(51.3–1002.3)	0.000
Anti-Jo-1 antibody	6(8.0)/75[g]	9(5.0)/181[g]	0.518
Pulmonary function test[f]			
FVC, predicted %	108.0 ± 15.6/25[g]	84.3 ± 20.6/83[g]	0.000
DLCO, predicted %	82.4 ± 15.5/25[g]	67.7 ± 20.7/83[g]	0.000
Comorbidities[f]			
Infection	17(20.0)	64(28.3)	0.136
IHD	6(7.1)	9(4.0)	0.406
CVD	4(4.7)	8(3.5)	0.884
Diabetes	14(16.5)	22(9.7)	0.098
Malignancy	6(7.1)	36(15.9)	0.030
Treatments			
Initial glucocorticoiddose[h]	60(45–60)	60(40-60)	0.967
Methotrexate[i]	42(49.4)	85(37.6)	0.059
Azathioprine[i]	15(17.6)	13(5.8)	0.001
Cyclophosphamide[i]	15(17.6)	51(22.6)	0.344
IVIG	25(29.4)	27(11.9)	0.001

Data are presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for abnormally distributed continuous variables and numbers (percentages) for categorical variables

[a] :Disease onset defined as the date of first symptom related to PM/DM

[b] :The time of recruitment defined as the date of first to our centre

[c] : Duration from disease onset to the first visit to our center

[d] : Duration from first visit to our center to death or last follow-up

[e] : Duration from disease onset to death

[f] : Present ever during course of disease

[g] : The second number is the 'denominator' and denotes the total number of patients in whom ANA, Anti-Jo-1 or pulmonary function was tested or ILD was confirmed

[h] : Presented as the dose of prednisone or equivalent (mg/day)

[i] : More than three months of treatment ever during course of disease

Abbreviations: ILD = interstitial lung disease; LDH = lactate dehydrogenase; HBDH = alpha-hydroxybutyrate dehydrogenase; CK = creatine kinase; FVC = forced vital capacity; DLCO = diffusing capacity of the lung for carbon monoxide; IHD = ischemic heart disease; CVD = cerebrovascular disease; IVIG = intravenous immunoglobulin

respectively, $p < 0.001$) (Fig. 3A)and the survival of all PM/DM patients with malignancy was lower than those without malignancy(70.9%, 60.2% and 50.0% vs. 88.8%, 83.2% and 78.9%, at 1, 5 and 10 years respectively, $p = 0.003$) (Fig. 3B).The significant differences were also observed between the patients with and without ILD(81.5%, 68.5% and 66.1% vs. 90.3%,

Table 2 SMR, LE and YLL in patients with PM and DM

	Overall $n = 331$	Females $n = 216$	Males $n = 95$
DM			
Total number	226	163	63
Total death number	55	37	18
Infection related death	34	23	11
ILD related death	25	19	6
Malignancy related death	14	7	7
SMR (95%CI)	9.0 (6.8–11.2)	12.0 (8.1–15.9)	6.0 (3.2–8.7)
SMR of patients with infection	25.5(6.1–23.8)	38.5 (22.8–54.2)	25.5 (17.5–33.6)
SMR of patients with ILD	10.4(6.6–14.2)	15.4(8.5–22.3)	5.1(1.0–9.2)
SMR of patients with malignancy	14.0(7.8–20.4)	8.2(2.1–14.3)	48.7(12.6–84.7)
LE of general population (years)	–	80.8	75.8
LE of DM patients(years)	–	43.3	47.4
YLL (years)	–	37.5	28.4
PM			
Total number	85	53	32
Death number	13	8	5
Infection related death	8	6	2
ILD related death	7	6	1
Malignancy related death	4	1	3
SMR (95%CI)	6.0 (3.5–8.5)	6.2 (2.8–9.6)	5.5 (0.7–10.2)
LE of general population (years)	–	80.8	75.8
LE of PM patients(years)	–	62.5	63.6
YLL (years)	–	18.3	12.2

Abbreviations: SMR = standardized mortality ratio; CI = confidence interval; LE = life expectancy; YLL = years of life lost; PM = polymyositis, DM = dermatomyositis

87.9% and 86.8%, at 1, 5 and 10 years respectively, $p < 0.001$) (Fig. 3C) as well as patients with and without infection (67.7%, 49.9% and 43.2% vs. 93.8%, 90.1% and 87.5%, at 1, 5 and 10 years respectively, $p < 0.001$) (Fig. 3D).

Causes of death

Among all the 68 deaths, we were unable to determine cause of death of 3 patients. The most common cause of death for the entire PM/DM patients was infection (52.3%) followed by malignancy (17.6%), and ILD (8.8%), while other less common causes in a descending order of the frequency were sudden death (4.4%), heart failure (2.9%), liver failure (2.9%), post-operative complication (1.5%), pneumothorax (1.5%), cerebral hemorrhage (1.5%), renal failure (1.5%) and pulmonary embolism (1.5%)(Table 3). There was no significant differences in the leading causes of death between PM and DM. In the group of patients who died from infection ($n = 34$),

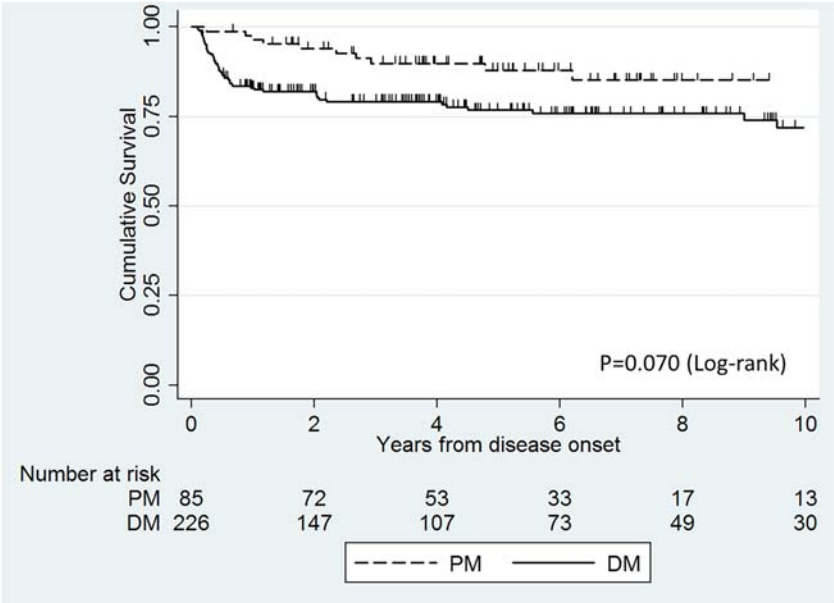

Fig. 2 Comparison of survival between PM and DM patients. The overall survival of the DM cohort was lower than the PM cohort, but there was no significantly statistical difference (77.4%, 75.8% and 73.9% vs 92.2%, 80.1% and 77.3%, at 1, 5 and 10 years respectively, $p = 0.349$, log rank). PM: polymyositis; DM: dermatomyositis;

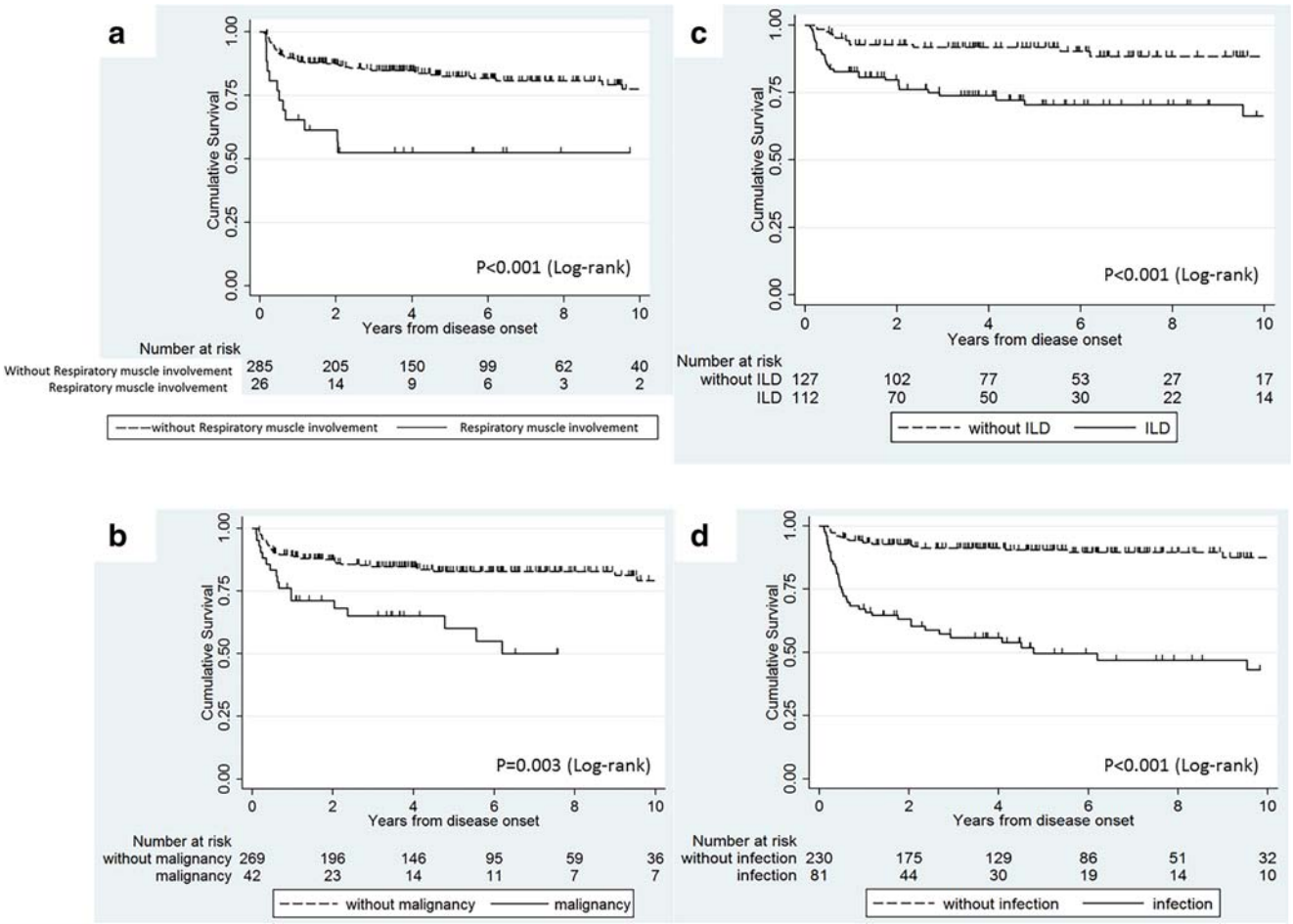

Fig. 3 Survival curves for PM/DM patients. (A) Survival curves for PM/DM patients with and without respiratory muscle involvement. (B) Survival curves for PM/DM patients with and without malignancy. (C) Survival curves for PM/DM patients with and withoutILD. (D) Survival curves for PM/DM patients with and without infection. ($P < 0.05$, log rank). PM: polymyositis; DM: dermatomyositis; ILD: interstitial lung disease.

Table 3 Cause of death

Cause of death Organ system	PM $N = 13$ n (%)	DM $N = 55$ n (%)	Overall $N = 68$ n (%)
Infection	5(38.5)	29(52.7)	34(50.0)
Malignancy	3(23.1)	9(16.4)	12(17.6)
ILD	2(15.4)	4(7.3)	6(8.8)
Sudden death	0(0)	3(5.5)	3(4.4)
Heart failure	1(7.7)	1(1.8)	2(2.9
Liver failure	0(0)	2(3.6)	2(2.9)
Post-operative complication	1(7.7)	1(1.8)	2(2.9)
Pneumothorax	0(0)	1(1.8)	1(1.5)
Cerebral hemorrhage	0(0)	1(1.8)	1(1.5)
Renal failure	0(0)	1(1.8)	1(1.5)
Pulmonary embolism	0(0)	1(1.8)	1(1.5)
Unknown	1(7.7)	2(3.6)	3(4.4)

Abbreviations: PM = polymyositis, DM = dermatomyositis, ILD = interstitial lung disease

pneumonia ($n = 29$) was the most common type, accounting for 38.5% in the 13 PM deaths and 43.6% in the 55 DM deaths. Lung cancer was the leading type in all patients who died from malignancy (66.7% in PM and 44.4% in DM).

Predictors of mortality

The univariable hazards analyses showed that age at disease onset, fever, heliotrope rash, respiratory muscle involvement, ILD, infection and malignancy carried a higher risk of death (all $p < 0.05$), whereas gender, disease duration at recruitment, Gottron's papule, mechanic's hand, arthralgia, cardiac involvement, serum CK level, anti-Jo-1 antibody, FVC, DLCO, hypertension and diabetes were found as insignificant predictors of mortality. Multivariate analysis revealed that age at disease onset (HR 1.04, 95%CI 1.02–1.06, $P < 0.001$), malignancy (HR 2.27, 95%CI 1.24–4.16, $P = 0.008$) and infection (HR 4.65, 95%CI 2.50–8.63, $P < 0.001$) were the independent predictors of mortality in PM/DM patients (Table 4).

Table 4 Cox regression analyses of risk factors in the DM/PM patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	p	HR	95%CI	P
Female	1.19	0.70–2.05	0.519			
Age at onset[a]	1.06	1.04–1.08	<0.001	1.04	1.02–1.06	<0.001
Disease duration at recruitment[b]	1.00	0.98–1.02	0.131			
Fever[c]	1.98	1.19-3.33	0.011	1.32	0.75–2.33	0.340
Gottron's papule[c]	1.39	0.84–2.31	0.205			
Heliotrope rash[c]	1.91	1.09–3.36	0.018	1.71	0.91–3.23	0.096
Mechanic's hand[c]	1.02	0.50–2.09	0.942			
Arthralgia[c]	0.86	0.33-1.29	0.203			
Respiratory muscle involvement[d]	3.12	1.69–5.78	0.001	1.37	0.71–2.66	0.347
Cardiac involvement[d]	1.65	0.40–6.79	0.517			
ILD[d]	2.03	1.22-3.39	0.007	1.10	0.54–1.66	0.842
CK[c]	1.00	1.00-1.00	0.967			
LDH[c]	1.00	1.00-1.00	0.149			
HBDH[c]	1.00	1.00-1.00	0.063			
Anti-Jo1 antibody	0.29	0.42–2.07	0.123			
FVC, predicted % [d]	1.02	0.98–1.06	0.301			
DLCO, predicted %[d]	1.02	0.98–1.07	0.312			
Hypertension[d]	1.44	0.84-2.47	0.195			
Diabetes[d]	0.84	0.38-1.85	0.648			
Infection[d]	6.68	3.90-11.44	<0.001	4.65	2.50–8.63	<0.001
Malignancy[d]	3.50	1.94-6.31	<0.001	2.27	1.24–4.16	0.008

[a] :Disease onset defined as the date of first symptom related to PM/DM

[b] : Disease duration defined as the time from onset of the first manifestation to first visit to our centre

[c] :Baseline clinical characteristics or laboratory examinations

[d] : Present ever during course of disease

Abbreviations: HR = Hazard Ratio; CI = confidence interval; ILD = interstitial lung disease; CK = creatine kinase; LDH = lactate dehydrogenase; HBDH = alpha-hydroxybutyrate dehydrogenase; FVC = forced vital capacity; DLCO = diffusing capacity of the lung for carbon monoxide

Discussion

Although some previous studies showed the poor prognosis of PM/DM [2–9, 24], data in terms of mortality of PM/DM with big patient population in China are limited. The present study is the first comprehensive report about the mortality situation in Chinese PM/DM patients. According to some previous reports, mortality of PM and DM patients varied within a range of 12.3–60.1% at 5 years, and the corresponding figures for 10 years varied between 42% and 74% [3–7]. In the present study, the mortality rate (21.9%) for PM/DM patients was in the middle of the reported number. The most common causes of death from other reports were heart or lung involvement, cancer, and infection [3–7]. In the present study, infection was the leading cause of death, which was the main difference of our cohort with most of the other cohorts. There are a few possibilities to explain the difference. Firstly, we suppose that environmental and socioeconomic factors may play important roles. Secondly, we found in the present study that patients who died in the early stage of disease more likely died of infection than those who died in the later stage of disease. We suspect that the higher mortality in the early stage may be associated with more intensive immunosuppression therapy. Some retrospective studies have shown that application of glucocorticoid and/or immunosuppressive agents were risk factors for infection in patients with PM/DM. [25–28].

In our cohort, there was a big difference in mortality between PM and DM patients. But the age and sex adjusted SMR of DM was much higher than that of PM (9.0 (6.8–11.2) vs.6.0 (95%CI 3.5–8.5)), and the YLLs of DM were also significantly more than the corresponding figures of PM both for women and men (37.5 years vs.18.3 years for women, and 28.4 years vs. 12.2 years for men) (Table 2). The overall survival in the first decade of disease in the DM cohort tended to be lower than that

in the PM cohort (81.5%, 76.6% and 71.7% vs. 94.6%, 87.5% and 84.8%, at 1, 5 and 10 years respectively, $p = 0.070$) (Fig. 2). The difference of mortality between PM and DM is consistent with the results of the other studies [2–9, 24], and it could be partly due to the higher proportions of patients complicated with malignancy and respiratory muscle involvement in DM than PM (15.9% vs.7.1% for malignancy and 10.2% vs. 3.5% for respiratory involvement) (Table 1). Meanwhile, the comparison between PM and DM patients who died revealed that the age at death of DM patients was much younger than that of the PM patients (59.2 ± 14.4 years vs. 69.4 ± 12.5 years; $P = 0.022$), and the disease duration at death of DM patients was much shorter than that of the PM patients (0.5 (0.2–2.0) years vs. 2.7(1.1–8.5), $p < 0.001$). The Kaplan-Meier analyses also showed that the survival curve of the DM patients decreased more quickly than that of the PM patients in the first year of disease onset. A Swedish cohort study also found that the 10-year survival curve descended most rapidly during the first year after diagnosis [3]. Therefore, close monitoring and appropriate management are particularly needed for DM patients, especially in the early stage of disease.

Pulmonary involvement including ILD and respiratory muscle involvement is the most common organ involvement in PM/DM patients, which occurred in 34.1% of PM and 48.2% of DM patients in our cohort. The association of pulmonary involvement with morbidity and mortality is more significant than that of muscle and skin lesion themselves [29, 30]. In the present study, ILD, which was almost equally distributed among the PM and DM patients (30.6% in PM and 38.1% in DM), had a significant impact on the patients' prognosis. The age and sex adjusted SMR of DM patients with ILD was 10.4, which was higher than that of the overall DM patients. The Kaplan-Meier analysis also showed that the patients with ILD had a significantly worse survival than the patients without ILD (66.1% vs.86.8% at 10 years). Respiratory muscle involvement is another severe pulmonary complication which was observed more often in the DM patients in our cohort, with the 10-year survival of 50% only. Univariate hazards regression analyses found that both ILD and respiratory muscle involvement were risk factors for mortality, which were also reported by some previous studies [29, 30]. Therefore, close monitoring and effective treatment are necessary for patients with these two types of pulmonary involvements.

An association between PM/DM and malignancy has been widely reported [2–8]. In the present study, there were 42 (13.5%) patients complicated with malignancy (6(7.1%) in PM and 36(15.9%) in DM), which was similar to the data from a Europa study [2].The author pointed out that malignancy occurred in 13% (374/2788) of cases, DM cases had a higher frequency of malignancy. It is not surprising that the patients with malignancy had a very poor prognosis. The SMR of this group of patients was as high as 14.0 and the 10-year survival was less than 50%, which was very similar with the result from a Spanish study where the SMR was 13.7 (95% CI11.3–16.5) compared to the Spanish general population [4]. The hazards regression analyses revealed that malignancy was an independent risk factor for mortality. Lung cancer was the most common type of malignancy (21.4%) in our cohort, followed by breast cancer (19.0%) and colon cancer (9.5%). These three types of cancer were also the most common types in the general population in China [31]. Lung cancer was also the most common type of cancer associated with PM/DM in western countries according to some previous studies [1, 2], but in Southeast Asian countries, nasopharyngeal cancer was the most common type of cancer associated with PM/DM [24].

Although pulmonary involvement and malignancy had strong impact on the patient's prognosis, we found that instead of malignancy and ILD, infection was the leading cause of death in both PM and DM patients accounting for half of the total deaths, which was different from the reports in western countries where malignancy was the leading cause of death [2, 3]. Infection was the strongest independent risk factor of mortality with HR of 4.65 (2.50–8.63). An article from China also found that lung infection is the strongest predictor of poor prognosis with HR of 5.63 (2.37–13.36) in PM/DM patients [32].The SMR of DM patients with infection was as high as 25.5 and the survivals of patients with infection were just 67.7%, 49.9% and 43.2% at 1,5 and 10 years respectively, and the survival curve went down fast in particularly during the first 5 years of disease onset, which means relatively more patients died in the early stage of disease. In fact, infection happened in 20.0% of PM patients and 28.8% of DM patients during their disease course, which were similar to other previous reports [32–34]. In Wu C et al' study, the three most frequent death causes for PM/DM patients were lung infection (34.9%), ILD exacerbation (20.6%), or both (25.4%) [32].Therefore, we suppose that environmental and socioeconomic factors may play important roles. In terms of economic development and healthcare level, there is significant imbalance in different geographic areas and administrative regions in China. The economic income of people in different social hierarchies also has big gaps. Some patients who live in remote villages or poor economic conditions do not have access to good sanitary and hygienic conditions. They are not able to have a regular follow up for their chronic disease, or have a prompt diagnosis/treatment if they are complicated with infection due to inadequate medical services. In terms of environmental factors, air pollution has been serious in some cities in China in recent years,

especially in those cities with heavy industry. Meanwhile, some patients may be involved in poor working environment, which increase the chances of getting infection. In addition, antibiotic abuse still exists in many hospitals in China and therefore drug-resistant nosocomial infections are still common. Secondly, we found in the present study that patients who died in the early stage of disease more likely died of infection than those who died in the later stage of disease. We suspect that the higher mortality in the early stage may be associated with more intensive immunosuppression therapy. Some retrospective studies have shown that application of glucocorticoid and/or immunosuppressive agents were risk factors for infection in patients with PM/DM [25–28]. However prospective controlled trials comparing the use of immunosuppressive agents and the incidence of infections in PM/DM remain rare. In our study, IVIG was used in 29.4% of PM patients and 11.9% of DM patients, mainly in severe cases and cases with secondary immune deficiencies. The immune-modulatory actions of IVIG have been recognized by previous studies [35–39]. Interestingly, the present study found that IVIG was associated with increased infection rate, which conflicted with the previous reports. But establishing a causal relationship between infections and IVIG is difficult, given the retrospective nature of this study. The observed association between infection and IVIG usage might be due to higher risks of infection in those patients receiving IVIG. Further investigations for the risk factors of infection in Chinese PM/DM patients are needed.

Our study showed that infection was the leading cause of death (34 patients, 52.3%). Among the 311 PM/DM patients, 81 (26.0%) developed major infections with a total of 104 episodes: 60 (74.1%) patients experienced one infectious episode and 21 (25.9%) had two or more episodes. In terms of pathogens, Candidiasis (20/104, 19.2%), Klebsiella (15/104, 14.4%), *Staphylococcus aureus* (14/104, 13.5%), and pneumocystis jiroveci pneumonia (8/104, 7.7%) were the top four types (Supplementary Table 1). Although pneumocystis jiroveci pneumonia was relatively rarer than common pneumonia, it was associated with a very high mortality rate of87.5% in our study. Notably, pneumocystis jiroveci pneumonia only happened in DM patients in our cohort. Further studies are needed to investigate the possible reasons of DM patients being more susceptible to pneumocystis jiroveci pneumonia Table 4.

There are some limitations in the present study. We have refrained from including treatment in our analyses due to the potential bias in retrospective studies evaluating therapeutic effects and lack of accurate data on the indication for, and the duration of treatment. Secondly, the number of PM patients was relatively small, especially in males, which may influence the accuracy of the calculation for mortality. A multi-center prospective cohort study will more accurately quantify mortality and evaluate the impact of treatment on mortality in PM/DM patients. Thirdly, the Bohan and Peter criteria was the most widely used criteria in clinical practice and scientific research in the past decades, and we also used it as the inclusion criteria in the present study. But the criteria has some limitations such as it's relatively lower sensitivity and classification accuracy. Nowadays, other sets of criteria such as the2017 criteria from EULAR/ACR are available [40], and they may overcome some of the limitations of Bohan and Peter criteria. But as a retrospective study, almost the diagnosis for all our patients were made according to Bohan and Peter criteria; therefore it is difficult for us to re-evaluate every single patient using other criteria.

In conclusion, this study confirmed the high mortality rate in Chinese PM/DM patients, with infection as the leading cause of death. There were a high prevalence of malignancy and ILD, both of which were associated with a reduced survival. Older age at PM/DM onset, malignancy and infection were significantly associated with mortality. The presence of poor prognosis factors prompts close follow-up and more appropriate management in patients with PM/DM.

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Data availability The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Ethics approval and consent to participate The ethics approval was obtained from the human research ethics committees of Peking University First Hospital.

Disclosures None.

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