

# Characteristics and predictors of malignancy in dermatomyositis: Analysis of 239 patients from northern China

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Received January 22, 2018; Accepted August 10, 2018

DOI: 10.3892/ol.2018.9409

**Abstract.** The present study aimed to determine the characteristics of patients with dermatomyositis (DM) in order to identify predictors of cancer in these patients. Data of 239 patients with DM, treated at Yuhuangding Hospital between 1997 and 2016, was retrospectively assessed. The patients' demographic, clinical, survival and laboratory data were analyzed. Of the 239 patients, 43 developed malignancies. In 30 (69.77%) patients, the malignancy was detected within 1 year before or after DM diagnosis. There were 15 (34.88%) fatalities. Lung cancer was the most common type of malignancy identified (n=6, 13.95%), and adenocarcinoma was the most common pathological type (n=6, 13.95%). Older age, absence of interstitial lung disease, and absence of arthralgia were demonstrated to be independent risk factors for malignancy. Myositis-specific autoantibody expression, specifically anti-TIF1 $\gamma$  positivity and/or anti-MDA5 negativity, was associated with cancer in patients with DM. The survival rate was significantly lower in patients with malignancy than in patients without malignancy. Patients with DM had a high incidence of malignancy and a poor prognosis. Lung cancer and adenocarcinoma are common among patients with DM in northern China. Cancer screening should be conducted in all DM patients, particularly within 1 year of DM diagnosis. Older age is a risk factor for malignancy in DM patients, while interstitial lung disease and arthralgia are protective factors. Myositis-specific autoantibody detection may be useful for cancer screening in patients with DM.

## Introduction

Dermatomyositis (DM) is a rare idiopathic inflammatory myopathy (IIM) (1). In 1916, Stertz (2) reported for the first time that IIMs are associated with malignancy. The overall malignancy risk is high in patients with IIM, particularly DM, compared with age- and sex-matched controls (3,4). Malignancy is usually diagnosed within 1 year after the diagnosis of DM and is a major cause of mortality among patients with DM (5). This implies that cancer may be dormant at the time of DM diagnosis, therefore, extensive evaluation of cancer-associated symptoms is recommended for patients with DM (6). However, numerous patients do not undergo a thorough cancer screening owing to financial constraints and the risk of iatrogenic impairment (for example, exposure to large doses of X-ray radiation) (1). Furthermore, the optimal frequency and intensity of cancer screening in DM patients remain undefined (4).

The majority of early epidemiological studies that describe the clinical characteristics of IIMs and their association with cancer were conducted in Western countries (7-9). These studies suggest that older age, male sex, elevated erythrocyte-sedimentation rate (ESR), dysphagia and cutaneous necrosis, among others, are risk factors for malignancy in patients with DM. The type of malignancy also varies among patients, and adenocarcinoma of the ovary, lung, or gastrointestinal tract, melanoma and non-Hodgkins lymphoma are the most common types of malignancy among patients with DM in Western countries (10,11). In contrast, nasopharyngeal cancer is the predominant cancer associated with DM in Asian regions, including Hong Kong, Taiwan, southern China, and southeast Asia, as well as in north Africa; other types of cancer that are common in these regions are cancers of the lung, breast, stomach, ovary, liver and lymph nodes (5,12,13). Thus, the distribution of malignancy varies with geographic region and ethnicity. Recently, myositis-specific autoantibodies (MSAs) have been investigated as potential predictors of malignancy in patients with DM. DM patients who test positive for anti-translation initiation factor (TIF)1 $\gamma$  and negative for anti-melanoma differentiation-associated (MDA)5 have been demonstrated to have an increased risk of malignancy (14). However, few large case studies have been conducted on this topic because DM is a rare disease. Furthermore, early studies have

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**Key words:** dermatomyositis, malignancy, risk factors, age, myositis-specific autoantibodies

achieved conflicting results (4), and data from China are relatively limited. Therefore, in the present study, long-term follow-up clinical data of 239 patients with DM from a single institution in northern China were analyzed to identify predictors of malignancy in DM.

## Materials and methods

**Patients.** Data was collected from 239 patients with DM who had been admitted to Yuhuangding Hospital affiliated to Qingdao University (Yantai, China) between 1997 and 2016. DM was diagnosed according to the Bohan and Peter criteria (15). Electromyography was used for 105 patients, and muscle biopsy had been performed in 163 patients. The patients were categorized into two groups according to the presence or absence of malignancy. As the criteria for DM in young and adult patients are different, we excluded patients with juvenile DM (<17 years old). The study was approved by the ethics committee of Yantai Yuhuangding Hospital, Qingdao University (Yantai, China; approval number: 2016-176).

**Data collection.** All data, including demographic, clinical and laboratory data, reported in this retrospective inception cohort study were obtained from hospital records. The following parameters were assessed: age at onset, sex, clinical features [hypertension, diabetes, smoking, interstitial lung disease (ILD), myalgia, proximal muscle weakness, dysphagia, dyslalia, skin changes, periungual erythematous, nail cuticle hypertrophy, mechanic's hand, Raynaud phenomenon, arthralgia and lymphadenectasis], laboratory data at the time of DM diagnosis [lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST), ESR, C-reactive protein (CRP), immunoglobulin G (IgG), anti-Jo1 antibody, ferroprotein, cancer antigen (CA)153, CA125, CA199, carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE)], mortality rate, cause of mortality, timing of tumor diagnosis, tumor type and pathological classification. ILD was diagnosed using both chest radiography and high-resolution computed tomography of the lung, and manifested as a ground-glass opacity, a reticular shadow, an irregular linear opacity, traction bronchiectasis, a cyst or a subpleural curvilinear shadow (16). All patients were followed up until mortality, loss to follow-up or 1 October 2017.

**Statistical analysis.** Between-group comparisons of normally distributed measurement data were conducted using Student's t-test or the Mann-Whitney U-test. The  $\chi^2$  test was used to analyze differences baseline characteristics data. To identify independent risk factors, the odds ratio (OR) and 95% confidence intervals (CI) were analyzed using multivariate Cox proportional hazards regression analysis. Variables with  $P < 0.05$  in univariate analysis were analyzed by multivariate analysis. Patient survival was analyzed using the Kaplan-Meier curve and the log-rank test. All statistical analyses were carried out using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). The results are reported as the median [interquartile range (IQR)].  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Demographic data.** Of the 239 patients with DM, 161 (67.36%) were women and 78 (32.64%) were men. The median age of the patients at the time of DM onset was 58 years (IQR, 53.00-67.75 years). There were 42 smokers (17.57%), 55 patients with hypertension (23.01%), 26 with diabetes mellitus (10.88%), and 115 with ILD (48.12%). A total of 48 fatalities occurred during the study period. The median follow-up duration was 38.00 months (16.50-75.00 months). The patients were divided into two groups: 43 patients with malignancies (17.99%), and 196 patients without malignancies (82.01%). The patients with malignancies were significantly older than those without malignancies [59.00 years (53.50-73.00) vs. 57.50 (48.00-62.50 years);  $P = 0.003$ ]. The demographic characteristics of the two groups are presented in Table I.

**Clinical data of patients with malignancies.** Of the 43 DM patients with malignancies, 18 were men, and 25 were women. A total of 15 of these suffered fatality. Lung cancer was the most common type of malignancy, present in 6/43 (13.59%) patients. Other malignancies included breast cancer ( $n = 5$ , 11.63%), gastric cancer ( $n = 5$ , 11.63%), colorectal cancer ( $n = 5$ , 11.63%), ovarian cancer ( $n = 4$ , 9.30%), nasopharyngeal cancer ( $n = 4$ , 9.30%), thyroid cancer ( $n = 3$ , 6.98%), cervical cancer ( $n = 2$ , 4.65%), and non-Hodgkins lymphoma, hepatocellular carcinoma, leukemia, spinal tumor, laryngocarcinoma, melanoma, esophageal cancer, fallopian tube carcinoma and esophageal cancer ( $n = 1$  for each type, 2.33%). The most common type of malignancy among women was breast cancer ( $n = 5$ , 20.00%), followed by ovarian cancer ( $n = 4$ , 16.00%) and lung cancer ( $n = 4$ , 16.00%). Nasopharyngeal cancer, gastric cancer and colorectal cancer were the most common types of cancer among men ( $n = 3$  for each type, 15.79%), followed by lung cancer ( $n = 2$ , 10.52%). The incidence of cancers detected before or after DM diagnosis is illustrated in Fig. 1. Overall, 30 cases of malignancy (69.77%) were detected within 1 year before or after DM diagnosis. Malignancy was detected at the time of the DM diagnosis in 12 (27.91%) patients, after DM diagnosis in 19 (44.19%) patients, and before DM diagnosis in 12 (27.91%) patients.

**Factors associated with malignancy.** Univariate analysis of risk factors in patients with DM with and without malignancy are presented in Tables I and II. The results demonstrated that the age of onset was significantly higher in patients with malignancy than in those without malignancy [59.00 years (53.50-73.00 years) vs. 57.50 years (48.00-62.50 years);  $P = 0.003$ ]. Furthermore, diabetes mellitus (23.26% vs. 8.16%;  $P = 0.005$ ) and the Gottron sign (69.77% vs. 63.78%;  $P = 0.049$ ) were significantly more common in the malignancy group than in the non-malignancy group. In contrast, ILD (18.6% vs. 54.59%;  $P < 0.001$ ), arthralgia (18.60% vs. 42.86%;  $P = 0.002$ ), and anti-Jo-1 antibody (0.00% vs. 9.18%;  $P = 0.041$ ) were significantly less common in the malignancy group than in the non-malignancy group. In addition, the levels of CA125 [14.65 U/ml (11.18-32.42 U/ml) vs. 12.95 U/ml (8.83-20.09 U/ml);  $P = 0.003$ ] and NSE [17.07 ng/ml (14.18-38.52 ng/ml) vs. 18.53 ng/ml (15.00-29.14 ng/ml);  $P = 0.021$ ] were significantly higher in

Table I. Baseline demographic characteristics of patients with dermatomyositis.

Variables	Overall	Malignancy	No malignancy	P-value
Cases, n (%)	239 (100.00)	43 (17.99)	196 (82.01)	-
Age (years)	58 (53.00-67.75)	59.00 (53.50-73.00)	57.50 (48.00-62.50)	0.003 <sup>a</sup>
Women, n (%)	161 (67.36)	25 (58.14)	136 (69.39)	0.109
Smoking, n (%)	42 (17.57)	12 (27.91)	30 (15.31)	0.059
Hypertension, n (%)	55 (23.01)	13 (30.23)	42 (21.43)	0.247
Diabetes, n (%)	26 (10.88)	10 (23.26)	16 (8.16)	0.005 <sup>a</sup>
ILD, n (%)	115 (48.12)	8 (18.60)	107 (54.59)	0.000 <sup>a</sup>
Mortality, n (%)	48 (20.08)	18 (41.86)	30 (15.31)	0.003 <sup>a</sup>

ILD, interstitial lung disease. <sup>a</sup>Significant difference between malignancy and no malignancy groups.

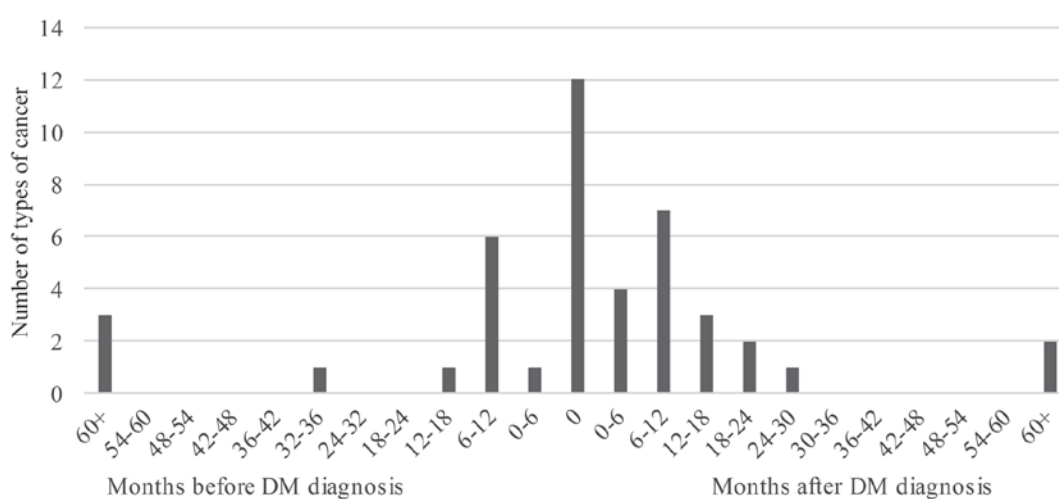


Figure 1. Temporal association between the diagnoses of malignancy and DM. DM, dermatomyositis.

the malignancy group than in the non-malignancy group. The above factors were analyzed by Cox proportional hazards regression analysis to identify independent factors associated with malignancy. The multivariate analysis revealed that older age at onset ( $P=0.022$ ), absence of ILD ( $P=0.009$ ), and absence of arthralgia ( $P=0.034$ ) were independently associated with malignancy in patients with DM (Fig. 2 and Table III).

**MSAs associated with malignancy.** MSA detection was first performed at the study hospital in 2016; therefore, only 17 patients underwent MSA detection. A total of 5 patients tested positive for anti-TIF1 $\gamma$  antibody, 3 of whom had cancer (sigmoid colon adenocarcinoma, esophageal cancer and nasopharyngeal carcinoma). A total of 4 patients were positive for anti-MDA5 antibody; none of whom had tumors, but all had ILD. A total of 3 patients were positive for anti-NXP2, and none of them had tumors. Among the 4 patients who underwent MSA testing and had cancer, 3 (75%) were positive for anti-TIF1 $\gamma$ , and 1 (with breast cancer) was positive for anti-RO-52. One patient with cancer was positive for both anti-TIF1 $\gamma$  and anti-SRP. Among the 13 patients with DM without tumors, 6 were positive for anti-RO-52, 2 for anti-SRP, and 2 for both anti-Mi-2 $\alpha$  and anti-Mi-2 $\beta$ . In addition, the patients without tumors were positive for anti-Ku or

anti-PL-7. The detailed results of the MSA tests are provided in Table IV.

**Survival analysis.** Of the 239 patients with DM, 48 mortalities occurred during the follow-up period (20.08%). The mortality rate was significantly higher in patients with malignancy ( $n=18$ , 41.86%) than in those without malignancy ( $n=30$ , 15.31%;  $P=0.003$ ). The presence of malignancy was inversely associated with the survival rate. Fig. 3 depicts the survival curves for patients with DM with or without malignancy. Kaplan-Meier survival curves showed that the survival rate was significantly lower in patients with malignancy than in patients without malignancy ( $P=0.001$ ; Fig. 3). The 1-, 5- and 10-year overall survival rates were 88.70, 85.36 and 80.33%, respectively. The cumulative survival rates in the malignancy group were 81.40% at 1 year and 58.14% at 5 years.

## Discussion

Our study demonstrated that DM was associated with a high risk of malignancy, which frequently developed within 1 year of DM diagnosis. The association between DM and malignancy is well documented; DM can occur at the same time as, before, or after cancer diagnosis (3,4,16,17). The

Table II. Univariate analysis of factors potentially associated with malignancy in patients with dermatomyositis.

Variables	Malignancy (n=43)	No malignancy (n=196)	P-value
Muscle pain, n (%)	26 (60.47)	114 (58.16)	0.91
Proximal muscle weakness, n (%)	23 (53.49)	129 (65.82)	0.141
Dysphagia, n (%)	16 (37.21)	46 (23.47)	0.077
Dysphonia, n (%)	7 (16.28)	28 (14.29)	0.783
Heliotrope rash, n (%)	21 (48.84)	109 (55.61)	0.343
Shawl rash, n (%)	19 (44.19)	60 (30.61)	0.109
V-shaped rash, n (%)	21 (48.84)	65 (33.16)	0.069
Gotttron papules, n (%)	30 (69.77)	125 (63.78)	0.049 <sup>a</sup>
Pruritus, n (%)	25 (58.14)	83 (42.35)	0.081
Poikiloderma, n (%)	9 (20.93)	32 (16.33)	0.511
Periungual erythema, n (%)	6 (13.95)	30 (15.31)	0.779
Nail cuticle hypertrophy, n (%)	2 (4.65)	9 (4.59)	0.989
Mechanic's hand, n (%)	12 (27.91)	67 (34.18)	0.378
Raynaud phenomenon, n (%)	1 (2.33)	15 (7.65)	0.196
Arthralgia, n (%)	8 (18.60)	84 (42.86)	0.002 <sup>a</sup>
Lymphadenectasis, n (%)	5 (11.63)	26 (13.27)	0.734
CK-MB, ng/ml (0-4.94)	13.57 (3.95-47.86)	6.77 (2.21-32.00)	0.612
AST, IU/l (15-40)	61.00 (31.5-144.5)	58.00 (32.25-118.00)	0.945
CPK, IU/l (40-200)	444.00 (99.00-2810.00)	209.00 (74.75-1401.75)	0.084
LDH, IU/l (120-250)	437.90 (334.00-680.00)	368.50 (262.50-514.50)	0.76
ESR, mm/h (0-15)	22.00 (12.75-28.50)	27.00 (16.00-46.00)	0.06
CRP, mg/l (0-5.0)	6.05 (3.45-13.50)	6.55 (3.45-18.05)	0.955
IgG, g/l (7.0-16.0)	10.90 (9.09-14.80)	13.50 (10.38-16.83)	0.075
Anti-Jo-1 antibody, n (%)	0 (0.00)	18 (9.18)	0.041 <sup>a</sup>
CEA, ng/ml (0-5.0)	1.53 (1.11-2.78)	2.04 (1.09-3.75)	0.936
CA125, U/ml (0-35.0)	14.65 (11.18-32.42)	12.95 (8.83-20.09)	0.003 <sup>a</sup>
CA153, U/ml (0-25.0)	11.37 (8.78-16.79)	15.54 (11.51-22.65)	0.423
CA199, U/ml (0-39.0)	9.57 (5.71-18.70)	9.57 (5.22-18.93)	0.209
NSE, ng/ml (0-17.0)	17.07 (14.18-38.52)	18.53 (15.00-29.14)	0.021 <sup>a</sup>
Ferroprotein, ng/ml (13-150)	196.30 (137.90-502.60)	300.30 (156.85-719.15)	0.929

CK-MB, creatine kinase-MB; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; LDH, lactate dehydrogenase; ESR, erythrocyte-sedimentation rate; CRP, C-reactive protein; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; CA, cancer antigen.

<sup>a</sup>Significant differences between malignancy and no malignancy groups.

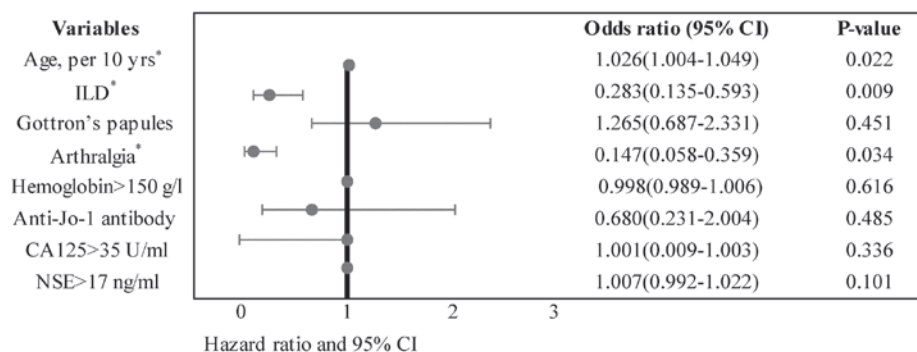


Figure 2. Multivariate analysis of factors associated with malignancy in patients with dermatomyositis. ILD, interstitial lung disease; CA125, cancer antigen 125; NSE, neuron-specific enolase; CI, confidence intervals. \*P<0.05.

precise association between DM and malignancy is unclear, but may include the following: i) DM may occur in the setting

of an immunological response to an internal malignancy; ii) there may be an increased risk of cancer in the setting of



Table III. Multivariate analysis of factors associated with malignancy in patients with dermatomyositis.

Variables	Odds ratio (95% CI)	P-value
Age, per 10 yrs	1.026 (1.004-1.049)	0.022 <sup>a</sup>
Diabetes	1.370 (0.527-3563)	0.773
ILD	0.283 (0.135-0.593)	0.009 <sup>a</sup>
Gotttron papules	1.265 (0.687-2.331)	0.451
Arthralgia	0.147 (0.058-0.359)	0.034 <sup>a</sup>
Hemoglobin >150 g/l	0.998 (0.989-1.006)	0.616
Anti-Jo-1 antibody	0.680 (0.231-2.004)	0.485
CA125 >35 U/ml	1.001 (0.009-1.003)	0.336
NSE >17 ng/ml	1.007 (0.992-1.022)	0.101

CI, confidence intervals; ILD, interstitial lung disease; NSE, neuron-specific enolase; CA125, cancer antigen. <sup>a</sup>Significant differences between malignancy and no malignancy groups.

immunosuppressive therapy for DM, and iii) detection rates may be increased in the setting of heightened surveillance after either diagnosis (18). It is difficult, in most cases, to determine whether a malignancy has contributed to the development of DM or whether DM has contributed to the development of a malignant tumor.

Older age was the only independent risk factor for malignant tumors in patients with DM, while arthralgia and ILD were protective factors. In our study, the incidence of malignancy among DM patients was 17.99%, which is consistent with previous reports from Western (8.6-32%) (1,5,17,19,20) and Asian countries (3.8-24.4%) (3,21-23). The most common malignancy in our study was lung cancer (n=6, 13.95%), followed by breast (n=5, 11.63%), gastric (n=5, 11.63%), colorectal (n=4, 9.30%), nasopharyngeal (n=4, 9.30%) and ovarian cancer (n=4, 9.30%). The risk of different types of cancer differs with geographic region and ethnicity. Within China, the incidence and mortality of nasopharyngeal carcinoma is higher in south China than in north China (24). In Western countries, lung, breast, and colorectal cancers are the most common types of cancer among DM patients (2,17,25). In a retrospective analysis from Scotland (17), the rates of cervical, ovarian and lung cancer were 12,10 and 5 times higher in DM patients than in the general population, respectively. After analyzing data from Sweden, Denmark and Finland, Hill *et al* (25) found that 32.04% patients with DM developed cancer, and that the most common types of malignancies were ovarian, lung, pancreatic, gastric and colorectal cancer, and non-Hodgkin lymphoma. The most common pathological type was adenocarcinoma. In a Tunisian study of 130 DM patients, 20 patients developed cancer, the majority of cases being breast (35%) and nasopharyngeal cancer (25%) (26). In a Portuguese study, prostate and colorectal cancers were the most prevalent (27). In a Japanese study, gastric, colorectal and ovarian cancers were the most common (28). Nasopharyngeal carcinoma is one of the most common types of cancer in southern China (22), Hong Kong (29), Taiwan (5), and Southeast Asia (12,30), and the most common DM-associated cancer in Asia (21).

The type of cancer also varied with sex, with breast cancer (n=5, 20.00%) being the most common type of cancer among women and nasopharyngeal, gastric and colorectal cancers (n=3 for each type, 15.79%) being the most common type among men. Adenocarcinoma was the most common pathological type in the present study. Therefore, we recommend that during cancer screening of DM patients, special attention must be paid to examinations of the lung, breast (in women) and digestive system (in men). The nose and throat should also be examined, and tests for the Epstein-Barr virus should be performed.

The incidence of cancer among patients with DM varied with the duration of DM. Cancer was detected within the first year after DM diagnosis in 53.49% patients, within 2-5 years in 17.28% patients, and after 5 years in 4.65% patients. The majority of cases of cancer (30/43, 69.77%) occurred within 1 year before or after the diagnosis of DM, which is consistent with previous reports (2,31,32). Recently, a large meta-analysis from Canada revealed that the standard incidence ratio of malignancy among DM patients was 17.29 (95% CI, 11.08-26.99) in the first year, 2.7 (95% CI, 1.96-3.72) from 2-5 years, and 1.37 (95% CI, 1.27-1.48) after 5 years (33). Some authors have reported that DM symptoms improved after successful tumor treatment and worsened with tumor recurrence (34,35). This parallel course of DM and malignancy suggests a paraneoplastic phenomenon (10). The findings of the present study emphasize the importance of tumor screening for DM patients, particularly in the first 5 years after diagnosis. The tumor risk remains high during the first 5 years, and, although it declines thereafter, it remains higher than the risk in the general population. Thus, we recommend that tumor screening in DM patients be continued for life.

The risk factors for malignancy in DM patients was also analyzed. Univariate analysis showed that older age, diabetes, Gotttron sign, hemoglobin, CA125 level and NSE were positively associated with malignancy, whereas joint pain, ILD, and anti-Jo-1 antibody were negatively associated with malignancy. In multivariate analysis, older age was the only independent risk factor for malignant tumors, and joint pain and ILD were protective factors. Older age has been proven to predict malignancy in patients with DM (1-5,17,19,22,23,27,33). Other reported risk factors include male sex, itching, skin necrosis, skin heterochromia, surrounding erythema, Gotttron sign, heliotrope rash, dysphagia, low albumin, elevated ALT, AST, LDH, ESR, CRP and CA125 levels, decreased complement C4 expression, elevated lymphocytes numbers, no response to cortisol therapy and rapid progression of skin and/or muscle changes (1,3-5,22,23,27,33). Protective factors include ILD, arthralgia, Raynaud phenomenon, anti-extractable nuclear antigen and anti-Jo-1 antibody (2,4,22). The association between CPK levels and risk of malignancy is controversial. Some authors (31,36) have reported that decreased CPK levels are associated with a higher risk of cancer, while others (1,2) have stated that increased CPK levels are associated with a higher risk of cancer. In the present study, CPK levels appeared to be increased in patients with malignancy than in those without malignancy, but the difference was not significant. In the present study, patients with DM with diabetes had a high risk of malignancy. To the best of our knowledge, this finding has not been previously reported. Epidemiological

Table IV. Clinical data of 17 patients who underwent tests for MSAs.

Patient no.	Sex	Age	Diagnosis	ILD	MSA
1	F	44	Breast carcinoma, DM	Y	Anti-R0-52+
2	F	74	Sigmoid colon adenocarcinoma, DM	N	Anti-TIF1 $\gamma$ +, anti-SRP+
3	M	79	Esophageal carcinoma, DM	N	Anti-TIF1 $\gamma$ ++
4	M	60	Nasopharyngeal carcinoma, DM	N	Anti-TIF1 $\gamma$ +
5	F	64	DM	Y	Anti-MDA5+, anti-Ku+, anti-R0-52 +++
6	F	45	DM	Y	Anti-MDA5++
7	F	45	DM	Y	Anti-MDA5++, anti-R0-52+
8	M	70	DM	Y	Anti-MDA5+++ , anti-R0-52++
9	M	51	DM	N	Anti-Mi-2 $\alpha$ +, anti-Mi-2 $\beta$ +
10	F	52	DM	N	Anti-Mi-2 $\alpha$ +, anti-Mi-2 $\beta$ ++
11	M	82	DM	Y	Anti-PL-7 $\pm$ , anti-R0-52+
12	F	56	DM	N	Anti-SRP+++ , anti-R0-52++
13	F	71	DM	N	Anti-TIF1 $\gamma$ +, anti-R0-52+++
14	F	47	DM	N	Anti-TIF1 $\gamma$ ++, anti-SRP+
15	F	27	DM	N	Anti-NXP2+
16	F	49	DM	N	Anti-NXP2+
17	F	20	DM	N	Anti-NXP2+

F, female; M, male; DM, dermatomyositis; MSA, myositis-specific autoantibodies; ILD, interstitial lung disease; Y, patients with ILD; N, patients without ILD; +, weakly positive; ++, positive; +++, strongly positive.

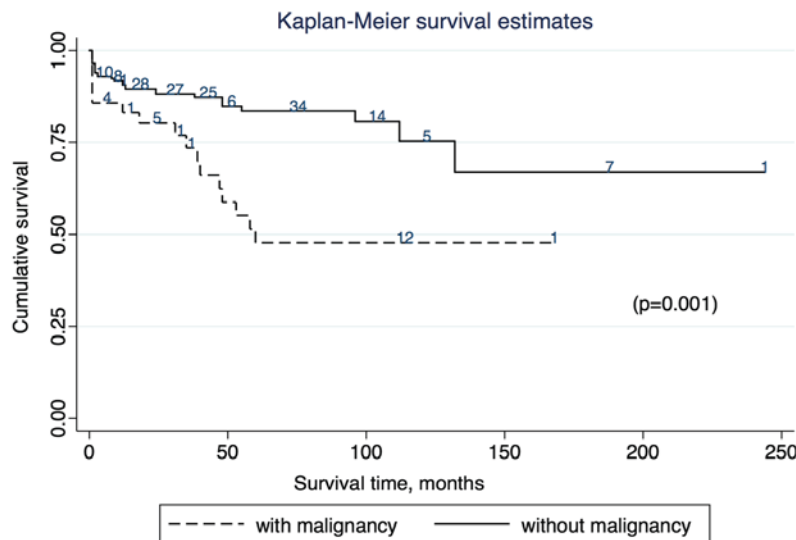


Figure 3. Cumulative survival curves for patients with dermatomyositis with (n=43) and without (n=196) malignancy.

evidence suggests an association between diabetes and increased cancer risk (37,38), **although the underlying pathogenesis remains unclear**. Possible factors include insulin resistance, hyperglycemia, impaired immune function and increased insulin levels due to hypoglycemic agents (39,40). The association between diabetes and risk of malignancy in DM patients will be investigated in future studies.

In recent years, MSAs have been evaluated in patients with DM, as these autoantibodies are often associated with distinct clinical phenotypes (41,42). In the present study, however, too few patients underwent MSA testing for us to be able to

conduct statistical analyses. One patient with sigmoid colon adenocarcinoma was positive for anti-TIF1- $\gamma$  antibody. DM patients positive for anti-TIF1- $\gamma$  and negative for anti-MDA5 antibodies may have an increased risk of malignancy. Between 50 and 100% DM patients with cancer have anti-TIF1- $\gamma$  antibodies (14,43-48). Dupont *et al* (49) revealed that TIF1- $\gamma$  is overexpressed in colonic adenocarcinoma. Anti-TIF1- $\gamma$  and anti-MDA5 antibodies are specific autoantibodies, which react with 155/140- and 140-kDa proteins, respectively, in patients with DM (43-46,50). Hoshino *et al* (14) found that anti-TIF1- $\gamma$  and anti-MDA5 antibodies do not co-exist in the same serum

sample, and that anti-MDA5 antibody-negative patients have a higher risk of developing malignancies than anti-MDA5 antibody-positive patients. Furthermore, the study showed that anti-MDA5 antibodies were associated with intractable ILD, particularly in patients with amyopathic DM. In the present study, there were 3 anti-NXP2-positive patients, none of whom had cancer. In a Japanese study (51), 3/7 anti-NXP2 antibody-positive patients with DM had malignancies (prostate, pancreatic and lung cancer). All patients were male with advanced cancer (stage IIIb-IV), but the study was insufficiently powered to definitively demonstrate a statistical association. Another study revealed that anti-NXP2 antibody was robustly associated with cancer, and with male sex (52). However, two more recent studies did not confirm this association (47,53). The controversy regarding this antibody highlights the importance of studying larger cohorts of patients to accurately delineate the association. Performance of MSA detection is limited at present, due to its unavailability in hospitals and its high cost. In a follow up study, we expect to include a large number of cases for which MSA detection is performed.

In the present study, the overall 5- and 10-year survival rates were 85.36 and 80.33%, respectively. The 5-year survival rate of DM patients with malignancy was 58.14%. The overall mortality rate was 20.08%, while the mortality rate in the malignancy group was 41.86%. These rates are consistent with previous findings. The reported 5- and 10-year survival rates of DM patients are 60-90.1 and 50-86.4% (20,54,55), respectively, while the 5-year survival rate of patients with DM and cancer is only 10-56% (26,31,32). The prognosis of patients with DM and cancer is worse than that of those without cancer, mostly because cancer is typically diagnosed at a late stage. The reported mortality rates for DM patients ranges from 16-75% (26).

In summary, patients with DM have a high incidence of malignancy, which reduces their survival rate. Thus, prompt screening for malignancies is required to enable early diagnosis and treatment, particularly within 1 year of diagnosis of DM. Older age was demonstrated to be a risk factor for malignancy, and the type of malignancy differed with sex and ethnicity. In the present study of patients from northern China, the risk of lung, breast, gastric, colorectal, ovarian and nasopharyngeal cancer was increased. Therefore, special attention must be paid to the lung, ear, nose, throat, breast, ovary and digestive system during cancer screening. In addition, expression of particular MSAs may predict cancer in patients with DM, thus, MSA testing should be performed in patients with DM.

## Acknowledgements

Not applicable.

## Funding

No funding was received.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

YLiu and HW conceived and designed the research. LX and NZ collected the data. XL and YLia analyzed the data. YLiu and YT performed the registration of follow-up data for all patients and contributed reagents, materials, and analysis tools. YT was responsible for assessing the disease and determining complications for all patients. YLiu wrote the paper. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Ethical approval was requested and obtained from the Ethics Committee of the Affiliated Yantai Yuhuangding Hospital of Qingdao University (Yantai, China). Written informed consent was obtained from all participants.

## Patient consent for publication

All participants provided written informed consent for the publication of this data and any associated images.

## Conflict of interest

The authors declare that they have no conflicts of interest.

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