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Analysis of risk factors of interstitial lung disease and mortality rates in Chinese patients with idiopathic inflammatory myopathy

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Abstract

Aim: To investigate the risk factors for interstitial lung disease (ILD) and prognosis in patients with idiopathic inflammatory myopathy (IIM).

Methods: A retrospective longitudinal study was performed in patients diagnosed with IIM between January 2012 and December 2018.

Results: The study cohort included 91 men and 195 women who were classified as having dermatomyositis (DM, n = 183), polymyositis (PM, n = 77), or clinical amyopathic DM (CADM, n = 26). ILD was identified in 46.5% (n = 133) of patients with IIM. The independent risk factors for ILD were age at disease onset, presence of anti-Ro-52 antibody, Gottron's papules, elevated serum immunoglobulin M levels and hypoalbuminemia. Older age at disease onset, ILD, malignancy, and increased serum aspartate aminotransferase and neutrophil-to-lymphocyte ratio (NLR) were identified as the independent predictors for mortality, whereas elevated serum albumin level was associated with a better prognosis. A total of 73 deaths (25.5%) occurred after a median follow-up time of 33 months. Infection (49.3%) was the leading cause of death. In the overall cohort, the 1-year, 5-year and cumulative survival rates were 83.2%, 74.2% and 69.4%, respectively. The receiver operating characteristic curve indicated that the optimal cut-off value of NLR for predicting death in IIM was 6.11.

Conclusion: IIM patients have a poor prognosis with substantial mortality, especially in patients who have older age at onset, ILD, malignancy and higher NLR. Close monitoring and aggressive therapies are required in patients having poor predictive factors.

KEYWORDS

dermatomyositis, idiopathic inflammatory myopathy, interstitial lung disease, polymyositis, prognosis

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1 | INTRODUCTION

Idiopathic inflammatory myopathy (IIM) is a heterogeneous group of autoimmune diseases mainly characterized by weakness in proximal extremities and elevated muscle enzyme levels, accompanied by the involvement of organs such as the lung and heart in addition to the joints and skin. Despite aggressive treatments, some refractory IIM patients have substantial morbidity and mortality, leading to increased risk of death and long-term disability. The 10-year mortality rate for IIM patients has been reported to range from 28.6% to 60.1%.[1-3] Myositis with pulmonary involvement is a main factor which affects the mortality of IIM patients and interstitial lung disease (ILD) is now a major cause of death in IIM patients.[4] Results from recent studies showed that age at disease onset, malignancy, infection, anti-melanoma differentiation-associated protein 5 (anti-MDA5) antibody, pneumomediastinum and Gottron's papules are the risk factors related to poor prognosis.[5-7] However, most of these studies focused on predictive indicators of mortality or ILD, whereas few multivariate survival analyses have investigated risk factors for ILD and death together. Moreover, data on the mortality rates of patients with IIM living in mainland China are limited. In the present study, a retrospective analysis was performed to assess mortality rates and causes of death across different clinical subsets, and determine prognostic factors related to ILD and mortality in a large cohort of Chinese patients diagnosed with IIM in a tertiary university hospital between 2012 and 2018. Due to the high heterogeneity of this autoimmune disorder, the prognosis of patients with IIM among different clinical subsets can widely vary. To obtain a comprehensive interpretation of the prognosis of IIM, patients having different myositis subtypes including dermatomyositis (DM), polymyositis (PM), and clinical amyopathic DM (CADM) were included. Data obtained from analysis of a relatively large sample cohort that includes more subclasses of myositis and longitudinal follow-up can contribute to a better understanding of the clinical characteristics that are associated with poor prognosis for patients with IIM.

2 | MATERIALS AND METHODS

2.1 | Patients

We consecutively selected 286 patients diagnosed with IIM who were hospitalized at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between January 2012 and December 2018. The inclusion criteria were: (a) age ≥16 years; (b) diagnosed with definite or probable DM/PM based on the criteria of Bohan and Peter;[8,9] (c) diagnosed with CADM based on the criteria of Sontheimer;[10] and (d) at least one follow-up visit to our center. The exclusion criteria included: (a) patients with muscle involvement due to infections, neuromuscular disease, metabolic endocrine disorders and myotoxic drugs; (b) inclusion body myositis; (c) patients diagnosed with another type of connective tissue disease; and (d) patients with incomplete primary data. All patients underwent high-resolution computed tomography (HRCT) at their first admission. Written informed consent was waived due to the retrospective nature of this study. The study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology in accordance with the principles of the Declaration of Helsinki (approval number: 2020-S105).

2.2 | Definitions

The diagnosis of ILD was based on the following criteria: (a) the presence of hallmark manifestations of disease including reticular, honeycombing, irregular linear or ground-glass opacities or patchy clouding on chest HRCT as judged by professional radiologists, pulmonologists or physicians;[11,12] (b) patients with ILD arising in response to definite exposure (eg, environmental, drugs) were excluded. The radiologic patterns of ILD were categorized into usual interstitial lung pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia (AIP) and undefined forms that were independently evaluated by 2 professional radiologists based on the American Thoracic Society/European Respiratory Society statement.[13,14] Patients were defined as having pulmonary infection according to distinctive infectious lesions in the lung as evaluated by radiologists or pulmonologists, positive etiological evidence (eg, sputum culture, bronchoalveolar lavage, blood culture, or pleural biopsy) as well as a good response to anti-infective treatments. Fever was documented as recurrent temperature >38°C without alternative explanations other than the primary disease. Antinuclear antibodies were considered positive at titers ≥1:100. Malignancies were defined as occurrence within 3 years before or after the diagnosis of IIM. Duration of disease was defined as the time from the date of the appearance of any symptoms associated with the primary disease to the date of the first visit to the rheumatology department. Methylprednisolone pulse therapy was defined as intravenous methylprednisolone ≥200 mg/d for 1-3 days.

2.3 | Methods

We retrospectively retrieved the medical records of 286 IIM patients to collect clinical data including demographic information, clinical features, laboratory parameters and therapeutic regimens and obtained the survival outcome of patients through follow-up. The patients were divided into an ILD group and non-ILD group according to the comprehensive evaluation by physicians at the first admission. To identify the mortality-related factors for IIM, the 286 patients were further divided into a survival group and deceased group. Clinical characteristics and laboratory parameters were compared between different subgroups. The data on survival outcome were obtained through telephone follow-up, and we attempted to contact cases who were lost to follow-up via correspondence or email. For patients who died at our hospital, the causes of death were identified via tracing of the medical records. To ascertain the date and cause of death for cases that were lost to

follow-up, family members were contacted by telephone or email. The antinuclear antibody profile for 6 autoantibodies was assessed by an immunoblotting assay using a EUROIMMUN kit (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany).

2.4 | Outcomes and follow-up

The primary end-point for this study was the all-cause mortality rate. Follow-up began at the index date, which was identified as the date of the first visit to our hospital. Follow-up ended at death, 30 November 2019, or the date the subject was lost to follow-up for any reason (eg, emigration), whichever date came first. The observation period was defined as the time from the index date to the last day of follow-up.

2.5 | Statistical analysis

Continuous variables are presented as mean ± standard deviation or as the median (quartile) depending on the normality of variables distribution. Continuous numerical variables of subgroups were compared with Mann-Whitney *U* test or Student's *t* test. Categorical variables were analyzed with Fisher's exact test or Chi-square test. Logistic regression analysis was conducted to investigate the risk factors for ILD. The survival rates of IIM patients were evaluated using Kaplan-Meier survival curves with log-rank test. The predictors associated with mortality were analyzed with Cox regression analysis. A receiver operating characteristic (ROC) curve was used to determine the best diagnostic threshold of the clinical index and evaluate the diagnostic efficacy. All data were analyzed using SPSS version 25.0 (IBM) and GraphPad Prism version 8.4 (GraphPad Software). A 2-tailed $P < .05$ was considered to indicate a statistically significant difference.

3 | RESULTS

3.1 | Epidemiologic characteristics and clinical manifestations

A total of 286 hospitalized patients diagnosed with IIM were enrolled. Of these, 183, 77 and 26 had DM, PM, and CADM, respectively. Among this patient group, 69% (195) were female and the mean age at disease onset was 49 ± 14 years with a median disease course of 4 months (range, 2-12 months). Nearly all (284/286) had at least one follow-up visit with a median duration of follow-up of 32 months (range, 1-103 months). Two patients were lost to follow-up. Baseline clinical characteristics of the ILD group and non-ILD group as well as the deceased group and survival group were compared (Table 1). The follow-up time of patients with ILD and the deceased group was significantly shorter than that of the control groups. Compared to the non-ILD group, patients with ILD exhibited a larger number of constitutional symptoms such as fever. The proportion of patients with pulmonary infection, arthralgia and Gottron's papules was significantly higher in the ILD group than the non-ILD group. Meanwhile, patients without ILD had a higher frequency of malignancy, myalgia and V sign compared with the ILD group. Out of the 133 patients with ILD, 127 could be assessed by HRCT. The distribution of radiologic patterns was: 43.3% NSIP (n = 55), 43.3% UIP (n = 55), 5.5% AIP (n = 7), 3.9% LIP (n = 5), 2.4% OP (n = 3) and 1.6% not defined (n = 2). There was no significant difference in ILD type in terms of clinical features and IIM subsets (Table S1). Pulmonary infection and ILD were predominantly observed in the deceased group (56% vs. 33% and 63% vs. 41%, respectively). A significant difference was observed in age at onset between the deceased group and survival group (54 ± 13 vs. 47 ± 13 years; $P < .001$). In terms of IIM subsets, the proportion of patients with DM in the deceased group was significantly higher than the survival group ($P = .001$). Patients in the deceased group exhibited a higher proportion of dysphagia (30% vs. 18%), heliotrope rash (58% vs. 32%), and Gottron's papules (59% vs. 43%) than the survival group. Compared with the survival group, the incidence of comorbidities such as hypertension and malignancy was significantly higher in the deceased group (Table 1).

3.2 | Laboratory features and treatment regimens

Baseline laboratory features and initial treatment modalities between different subgroups were compared (Table 2). The percentages of anti-Ro-52 antibody and anti-Jo-1 antibody were significantly higher in the ILD group than the non-ILD group. The levels of serum globulin, serum immunoglobulin G (IgG) and serum IgM in the ILD group were significantly higher than those in the non-ILD group, whereas the serum albumin level of patients with ILD was significantly lower. Compared to the survival group, the presence of anti-Jo-1 antibody, platelet count, lymphocyte count, serum total protein level and serum albumin level were significantly lower in the deceased group. Meanwhile, serum aspartate aminotransferase (AST) level, neutrophil-to-lymphocyte ratio (NLR) and erythrocyte sedimentation rate (ESR) were significantly higher in patients who died. In terms of initial therapy modalities, 81% of all the enrolled patients treated at our center received a combination treatment of glucocorticoids and immunosuppressants, with the most frequent being cyclophosphamide (32.2%), followed by methotrexate (29.0%), calcineurin inhibitors (19.2%), hydroxychloroquine (17.8%), intravenous Igs (16.1%), plasma exchange (15.4%) and azathioprine (9.8%). The proportion of patients treated with cyclophosphamide in the ILD group was significantly higher than the control group. Subgroup analysis by a Kaplan-Meier curve indicated that in the ILD group (n = 133), patients treated with methylprednisolone pulse appeared to show a higher mortality than those who did not receive methylprednisolone pulse (Figure 1A).

3.3 | Causes of death

Among the 73 deaths in the study group, no cause of death was known for 4 patients. The most common cause of death in our

TABLE 1 Baseline clinical characteristics between different subgroups, X ± SD, median (interquartile range) or n (%)

Characteristics	ILD group (N = 133)	Non-ILD group (N = 153)	*P* value	Deceased group (N = 73)	Survival group (N = 213)	*P* value
Gender (M/F)	44/89	47/106	.669	26/47	65/148	.419
Mean age at disease onset, y	50 ± 11	47 ± 15	.029*	54 ± 13	47 ± 13	<.001***
DM/PM/CADM	86/32/15	97/45/11	.353	59/8/6	124/69/20	.001**
Median duration of disease, mo	5 (2,12)	4 (2,12)	.669	4 (2,12)	4 (2,12)	.844
Median time of follow-up, mo	26 (13,54)	37 (20,61)	.007**	6 (2,16)	42 (25,66)	<.001***
Fever	54 (42)	43 (28)	.013*	29 (40)	70 (33)	.288
Pulmonary infection	65 (49)	47 (31)	.002**	41 (56)	71 (33)	.001**
ILD	133 (100)	0	/	46 (63)	87 (41)	.001**
Myalgia	60 (45)	88 (58)	.036*	36 (49)	112 (53)	.630
Muscle weakness	106 (80)	123 (80)	.884	61 (84)	168 (79)	.387
Arthralgia	69 (52)	61 (40)	.042*	34 (47)	96 (45)	.824
Dysphagia	22 (17)	38 (25)	.086	22 (30)	38 (18)	.026*
Heliotrope rash	47 (35)	62 (41)	.368	42 (58)	67 (32)	<.001***
Gottron's papules	72 (54)	63 (41)	.029*	43 (59)	92 (43)	.020*
V sign	28 (21)	49 (32)	.037*	20 (27)	57 (27)	.916
Shawl sign	24 (18)	30 (20)	.736	18 (25)	36 (17)	.144
Comorbidity						
Arterial hypertension	22 (17)	35 (23)	.181	21 (29)	36 (17)	.029*
Diabetes mellitus	16 (12)	23 (15)	.460	11 (15)	28 (13)	.679
Coronary heart disease	3 (2)	9 (6)	.127	5 (7)	7 (3)	.190
Malignancy	4 (3)	14 (9)	.033*	12 (16)	6 (3)	<.001***

Abbreviations: CADM, clinical amyopathic dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease; M/F, male/female; PM, polymyositis.
*$P < .05$.; **$P < .01$.; ***$P < .001$.

cohort was infection (49.3%), followed by ILD (19.2%) and malignancy (11.0%), while other less frequent causes were, in descending order, heart failure (6.8%), cerebral hemorrhage (2.7%), sudden death (1.4%), pulmonary embolism (1.4%), rhabdomyolysis (1.4%) and renal failure (1.4%) (Table 3). No significant differences in the leading causes of death were observed among the DM, PM and CADM subsets. Pneumonia was the most frequent condition in patients who died from infection (n = 32). Lung cancer was the leading condition in the group of patients who died from malignancies (n = 4).

3.4 | Survival analysis

Across the median follow-up time of 33 months, 73 (25.5%) deaths were observed in our cohort. The 1-year, 5-year and cumulative survival rates of the entire IIM cohort were 83.2%, 73.3% and 68.3%, respectively. After stratification by age, the Kaplan-Meier analysis revealed significantly lower survival rates in patients with disease onset at ≥60 years old than those who were younger than 60 years at disease onset (68.5% vs. 86.6%,, 49.1% vs. 78.4% and 36.9% vs. 74.1% for 1, 5 and cumulative years, respectively). Significant differences were also observed in patients with and without ILD (75.2% vs. 90.2%, 62.9% vs. 82.1% and 60.5% vs. 74.6% for 1, 5 and cumulative years, respectively) (Table 4). For IIM subsets, there were significant differences in survival rates among DM, PM, and CADM in 1, 5 and cumulative years ($P = 0.005$, $P = .001$ and $P = 0.001$, respectively). PM had the highest cumulative survival rate of up to 86.0%, followed by patients with CADM (76.9%) and DM (59.2%) (Figure 2H). Univariate analysis with the log-rank test demonstrated that the mortality rates of patients with pulmonary infection, malignancy, hypertension, dysphagia, heliotrope rash, Gottron's papules and absence of anti-Jo-1 antibody were significantly higher than the controls (Figure 2). For the classifications of ILD, the cumulative survival rates were 73.1% for NSIP, 58.6% for UIP, 0% for AIP, 60.0% for LIP, 100.0% for OP and 50.0% for the undefined, with a significant difference in log-rank test ($P < .001$) (Figure 1B).

3.5 | Prognostic factors for ILD and mortality

Univariate analysis showed there were 14 predictors related to the occurrence of ILD at the significance level of $P < .05$ (Table S2).

TABLE 2 Baseline laboratory features and treatment modalities between different subgroups, X ± SD, median (interquartile range) or n (%)

Baseline laboratory examinations	ILD group (N = 133)	Non-ILD group (N = 153)	*P* value	Deceased group (N = 73)	Survival group (N = 213)	*P* value
ANA	55 (43)	50 (34)	.132	26 (38)	79 (38)	.993
Anti-dsDNA antibody	1 (1)	1 (1)	.918	0	2 (1)	1.000
Anti-SSA antibody	26 (20)	20 (13)	.132	8 (12)	38 (18)	.222
Anti-SSB antibody	4 (3)	3 (2)	.564	2 (3)	5 (2)	.798
Anti-Ro-52 antibody	68 (53)	40 (27)	<.001***	24 (35)	84 (40)	.489
Anti-Jo-1 antibody	24 (19)	9 (6)	.001**	2 (3)	31 (15)	.009**
WBC, $\times10^9$/L	7.17 (5.09,10.99)	7.51 (5.52,10.00)	.530	7.96 (5.24,11.29)	7.39 (5.24,10.21)	.605
RBC, $\times10^9$/L	4.18 ± 0.55	4.14 ± 0.59	.548	4.08 ± 0.64	4.19 ± 0.55	.181
PLT, $\times10^9$/L	218 (164,282)	214 (162,274)	.692	188 (146,249)	227 (175,283)	.010*
Hb, g/L	121 ± 15	122 ± 19	.470	119 ± 18	123 ± 17	.116
Neutrophil count, $\times10^9$/L	5.61 (3.50,8.88)	5.64 (3.87,8.33)	.715	5.86 (4.17, 9.44)	5.52 (3.50, 8.38)	.172
Lymphocyte count, $\times10^9$/L	1.01 (0.73,1.56)	1.10 (0.76,1.65)	.337	0.84 (0.63, 1.23)	1.11 (0.83, 1.72)	<.001***
NLR	5.28 (3.21,8.79)	5.04 (3.18,8.28)	.605	6.88 (3.83, 12.76)	4.54 (2.86, 7.92)	<.001***
Total protein, g/L	65.7 (61.5,71.7)	66.7 (61.9,73.5)	.201	63.7 (59.7, 68.5)	66.8 (63.1, 74.4)	<.001***
Albumin, g/L	32.7 (29.5,35.4)	36.2 (32.6,40.3)	<.001***	31.8 (28.1, 34.2)	35.2 (32.0, 39.5)	<.001***
Globulin, g/L	33.6 (29.6,37.3)	31.1 (26.6,34.7)	.001**	32.5 (28.7, 35.6)	31.8 (27.6, 36.2)	.690
ALT, U/L	45 (23,96)	48 (23,107)	.750	48 (28,111)	46 (23,98)	.399
AST, U/L	56 (32,129)	65 (30,154)	.543	85 (35,174)	55 (27,137)	.031*
CK, U/L	376 (63,1610)	402 (64,2565)	.529	344 (67,1913)	442 (61,2371)	.451
LDH, U/L	402 (286,570)	394 (261,627)	.724	423 (303,661)	392 (270,566)	.212
ESR, mm/L	28 (15,49)	22 (10,39)	.021*	32 (16,49)	22 (12,40)	.018*
IgG, g/L	13.4 (11.0,17.5)	11.0 (8.8,14.0)	<.001***	12.1 (10.0,16.3)	12.0 (9.7,15.7)	.440
IgA, g/L	2.3 (1.6,3.1)	2.2 (1.5,2.8)	.194	2.3 (1.9,3.1)	2.1 (1.5,2.8)	.074
IgM, g/L	1.5 (1.0,2.1)	1.2 (0.9,1.8)	.023*	1.3 (0.9,2.1)	1.3 (1.0,2.0)	.968
C3, g/L	0.93 (0.80,1.16)	0.93 (0.83,1.16)	.831	0.91 (0.80,1.17)	0.94 (0.83,1.16)	.332
C4, g/L	0.27 (0.20,0.33)	0.27 (0.22,0.35)	.473	0.27 (0.22,0.33)	0.27 (0.21,0.33)	.931
Initial treatment regimens						
PE	21 (16)	23 (15)	.860	10 (14)	34 (16)	.644
High-dose glucocorticoid therapy	8 (6)	6 (4)	.413	5 (7)	9 (4)	.370
IVIG	24 (18)	22 (14)	.400	12 (16)	36 (16)	.924
GC alone	20 (17)	37 (24)	.048*	18 (25)	39 (18)	.374
GC+CTX	62 (47)	30 (20)	<.001***	25 (34)	67 (32)	.660
GC+FK506/CsA	28 (21)	27 (18)	.466	9 (12)	46 (22)	.083
Initial dose of oral glucocorticoid, mg	40 (40,50)	32 (40,50)	.266	40 (40,50)	40 (32,50)	.245

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase / glutamic-oxalacetic transaminase; CK, creatine kinase; CsA, cyclosporin; CTX, cyclophosphamide; ESR, erythrocyte sedimentation rate; FK506, tacrolimus; GC, glucocorticoid; Hb, hemoglobulin; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PE, plasma exchange; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

*$P < .05$.; **$P < .01$.; ***$P < .001$.

Variables with $P < .05$ in univariate logistic analysis were considered as candidates for entry into multivariate logistic regression. In the multivariate model, age at disease onset (odds ratio [OR] = 12.593 and OR = 21.211), the presence of anti-Ro-52 antibody (OR = 2.560), Gottron's papules (OR = 2.342) and the serum IgM level (OR = 1.930) were the independent risk factors for ILD, whereas baseline serum albumin level presented a protective effect (OR = 0.915) (Table 5).

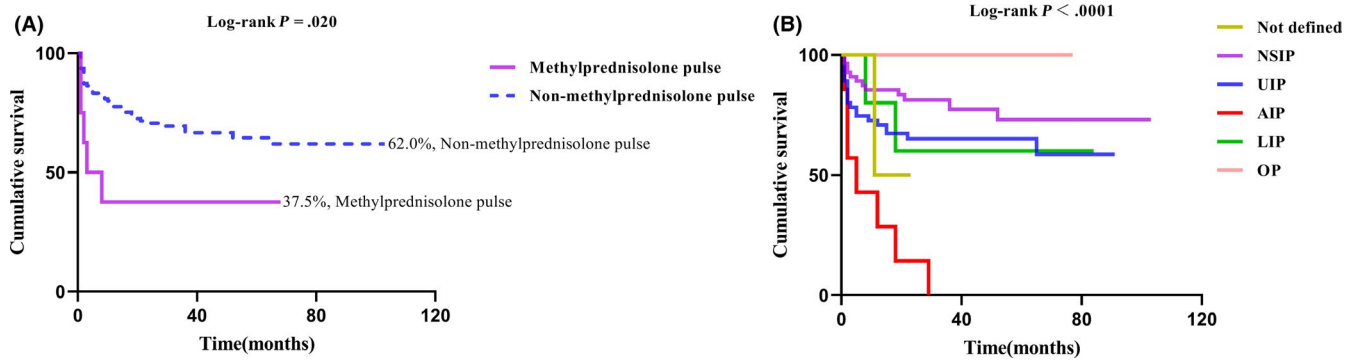

FIGURE 1 (A) Kaplan-Meier survival curves of patients in the interstitial lung disease (ILD) group treated or not with methylprednisolone pulse; (B) ILD group mortality rates according to radiologic classifications of interstitial lung disease. UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; AIP, acute interstitial pneumonia; OP, organizing pneumonia; LIP, lymphocytic interstitial pneumonia

Univariate Cox regression identified 16 mortality-related factors for IIM (Table S3). After adjusting for gender, age, comorbidities, laboratory parameters and IIM subsets, ILD (hazards ratio [HR] = 2.215) and malignancy (HR = 3.889) were independently associated with a poor prognosis. Mortality increased slightly with higher serum AST level (HR = 1.002), higher NLR (HR = 1.029) and higher age at disease onset (HR = 1.024), whereas the baseline serum albumin level (HR = 0.933) was associated with a favorable prognosis (Table 6). As displayed above, baseline NLR was identified as an independent risk factor for mortality. Therefore, the ROC curve analysis of NLR was performed to evaluate the predictive value of this factor for mortality. The ROC curve suggested the best diagnostic cut-off value of NLR for predicting death in IIM patients was 6.11 (Figure 3A). Kaplan-Meier curves further indicated that the survival rate of patients with NLR >6.11 was significantly lower than that of patients with NLR ≤6.11 (log-rank test <0.001) (Figure 3B).

4 | DISCUSSION

Although multiple studies have reported on predictors associated with prognosis and ILD in patients with IIM, the data regarding mortality of IIM subsets DM/PM/CADM in a relatively large study population in mainland China were limited. The present study investigated independent risk factors for ILD and poor prognosis of IIM patients. The 1-year, 5-year and cumulative survival rates of the overall cohort and the subgroups stratified by age, IIM subsets and ILD were also examined. To the best of our knowledge, our study represents the most comprehensive patient cohort comprising of 3 clinical subsets of IIM to determine both the risk factors for ILD and mortality.

Previous studies indicated that the frequency of IIM patients with accompanying ILD varied from 20% to 75%.[15-17] The ILD occurrence rate in this study, 46.5%, fell in the mid-range of this series. Similar to the meta-analysis by Hiroyuki et al.,[18] our study demonstrated that age at disease onset was an independent risk factor for ILD. This relationship is likely associated with the higher likelihood of comorbidities as well as reduced tolerance to disease due to diminished basal pulmonary function with age. Our data indicated that patients aged between 30 and 60 years and those over 60 years had 12.6-fold and 21.2-fold higher risk, respectively, for developing ILD than patients younger than 30 years. Our data also suggested that Gottron's papules are an independent risk factor for patients complicated with ILD, which is consistent with previous studies.[19] Therefore, careful screening for pulmonary parenchyma involvement should be performed, particularly for those patients who were over 30 years at disease onset and those who have Gottron's papules.

The myositis-associated autoantibody, anti-Ro-52 antibody was previously shown to be associated with ILD in IIM patients,[20,21] which is consistent with finding for this study. Our cross-sectional data demonstrated that the presence of anti-Ro-52 antibody could be a potential marker for ILD with an OR of 2.560. Anti-Jo-1 antibody was considered to be the strongest predictor of pulmonary fibrosis, although this possibility has become increasingly controversial in recent years.[21] In our cohort, multivariate analysis showed that anti-Jo-1 antibody was not an independent predictor of ILD, although the prevalence of anti-Jo-1 antibody was significantly higher in patients with ILD. These results suggest that anti-Ro-52 antibody has a higher predictive value relative to the anti-Jo-1 antibody in predicting ILD occurrence in IIM.

In our study, we revealed several serum biomarkers that were associated with increased risk for ILD and that were not analyzed in previous studies. Data from our cohort suggested that a higher level of serum IgM (OR = 1.930) was an independent predictor for ILD in IIM patients. The role of B cells in myositis pathogenesis has been supported by the presence of autoantibodies and favorable treatment responses to rituximab.[22] Thus, the elevated serum IgM levels seen in IIM patients with ILD may be indicative of inflammatory activation in B cells that could drive development of ILD, although prospective studies are needed to confirm whether IgM is simply an indicator of inflammation or whether IgM-producing B cells are directly affecting this condition. Multivariate analysis suggested that a reduction in serum albumin levels correlated with occurrence of ILD. According to a prior study, albumin, as a protective factor, can

TABLE 3 Comparisons of cause of death according to different idiopathic inflammatory myopathy subsets

Cause of death	DM N = 58 (%)	PM N = 9 (%)	CADM N = 6 (%)	Overall N = 73 (%)
Infection	30 (51.7)	4 (44.4)	2 (33.3)	36 (49.3)
ILD	10 (17.2)	1 (11.1)	3 (50.0)	14 (19.2)
Malignancy	7 (12.1)	0	1 (16.7)	8 (11.0)
Heart failure	4 (6.9)	1 (11.1)	0	5 (6.8)
Unknown	3 (5.2)	1 (11.1)	0	4 (5.5)
Cerebral hemorrhage	1 (1.7)	1 (11.1)	0	2 (2.7)
Sudden death	1 (1.7)	0	0	1 (1.4)
Pulmonary embolism	0	1 (11.1)	0	1 (1.4)
Rhabdomyolysis	1 (1.7)	0	0	1 (1.4)
Renal failure	1 (1.7)	0	0	1 (1.4)

Abbreviations: CADM, clinical amyopathic dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease; PM, polymyositis.

TABLE 4 Survival rates in subgroups and overall idiopathic inflammatory myopathy cohort

Group	Total (n=)	Death (n=)	1-year survival rates (%)	5-year survival rates (%)	Cumulative survival rates (%)	*P* value[a] (1 year)	*P* value[b] (5 year)	*P* value[c] (cumulative)
IIM	286	73	83.2%	73.3%	68.3%	-	-	-
The subgroups of age								
<60 years	232	48	86.6%	78.4%	74.1%	.002**	<.001***	<.001***
≥60 years	54	25	68.5%	49.1%	36.9%			
The subgroups of ILD								
ILD	133	46	75.2%	62.9%	60.5%	.001**	<.001***	.001**
Non-ILD	153	37	90.2%	82.1%	74.6%			
The subsets of IIM								
DM	183	59	78.1%	65.2%	59.2%	.005**	.001**	.001**
PM	77	8	94.8%	90.0%	86.0%			
CADM	26	6	84.6%	76.9%	76.9%			

Abbreviations: CADM, clinical amyopathic dermatomyositis; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; PM, polymyositis.

[a]*P* values for comparison of survival rates among different subgroups at 1 year of follow-up.

[b]*P* values for comparison of survival rates among different subgroups at 5 year of follow-up.

[c]*P* values for comparison of cumulative survival rates among different subgroups.

*$P < .05$.; **$P < .01$.; ***$P < .001$.

inhibit endothelial cell apoptosis, prevent the generation of oxygen free radicals and reduced platelet aggregation.[23] A large number of cytokines and inflammatory mediators are produced during the course of ILD that could lead to a decline in albumin synthesis in the liver. Consequently, pulmonary fibrosis could progress due to the weakened protective action of albumin and activation of fibroblasts. Moreover, in a study of 1269 patients with idiopathic interstitial pneumonia, David et al. found that hypoalbuminemia was independently associated with higher mortality.[24] Hence, close attention and effective treatments are necessary for IIM patients with hypoalbuminemia to avoid progression to ILD.

Earlier studies reported the mortality of IIM patients ranged from 10% to 45%.[25-28] In our study, the mortality of IIM patients was 25.5% across 7 years, which is in the mid-range of previously reported rates. In addition, previous studies showed that survival rates of IIM patients ranged from 79.3%-96%, 69.9%-93% and 67%-92% at 1, 5 and 10 years, respectively.[2,3,26,29,30] The 1-year, 5-year and cumulative survival rates of IIM patients in our cohort were 83.2%, 73.3% and 68.3%, respectively, which are on the lower end of these ranges. This discrepancy could be explained in part by ethnic differences among populations and different treatment regimens. Thus, multicenter studies are needed to determine the mortality rate of IIM patients from different regions.

In terms of predictors that influence survival, our study confirmed several clinical prognostic factors that were previously reported to be associated with mortality in IIM patients, such as age at onset, ILD and malignancy.[28,31,32] Malignancy is considered to be a severe complication of IIM patients and closely related to poor prognosis.[3]

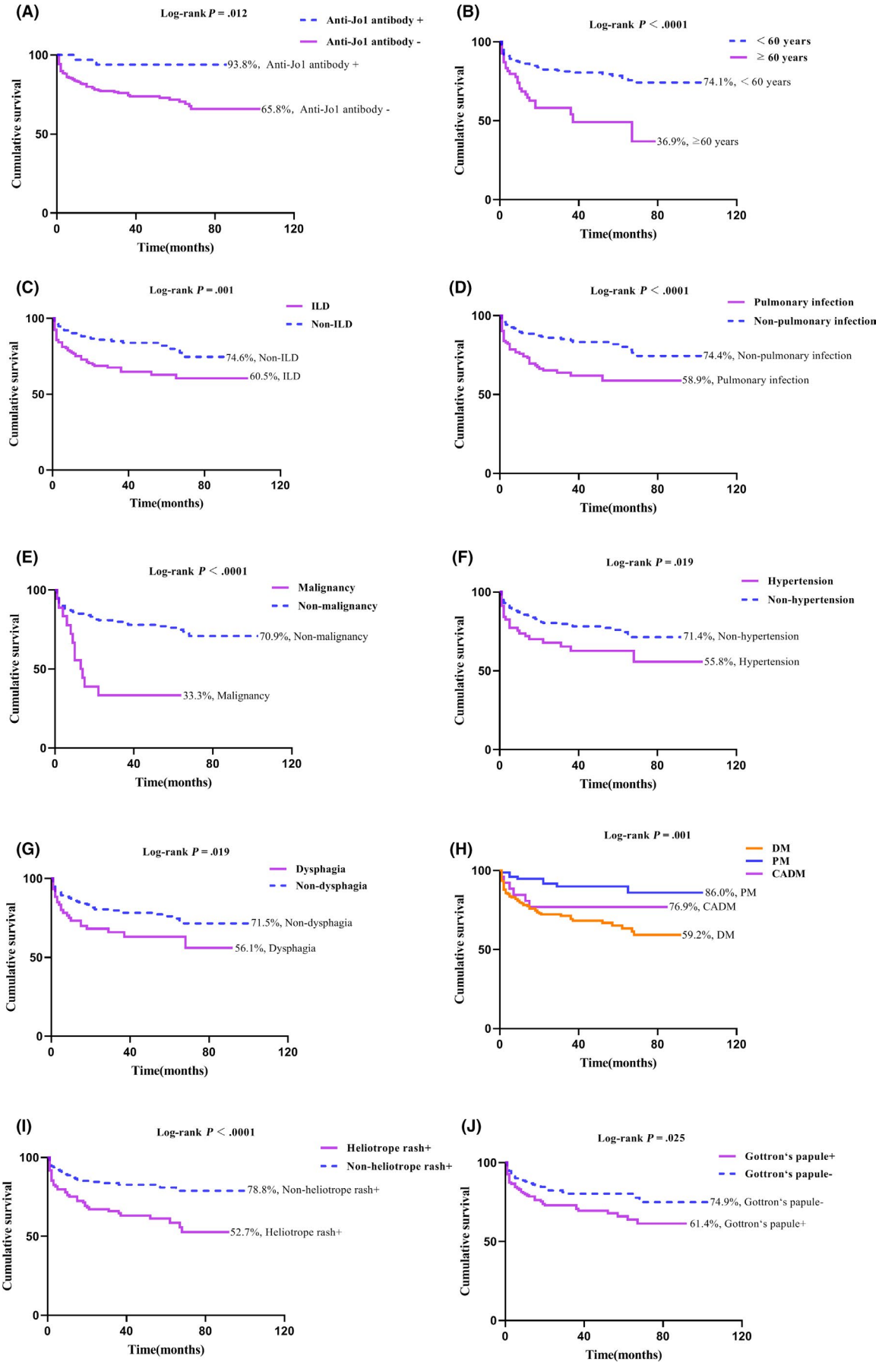
(A)
Log-rank P = .012
Anti-Jo1 antibody +
Anti-Jo1 antibody -
93.8%, Anti-Jo1 antibody +
65.8%, Anti-Jo1 antibody -
Cumulative survival
Time(months)
(B)
Log-rank P < .0001
< 60 years
≥ 60 years
74.1%, < 60 years
36.9%, ≥60 years
Cumulative survival
Time(months)
(C)
Log-rank P = .001
ILD
Non-ILD
74.6%, Non-ILD
60.5%, ILD
Cumulative survival
Time(months)
(D)
Log-rank P < .0001
Pulmonary infection
Non-pulmonary infection
74.4%, Non-pulmonary infection
58.9%, Pulmonary infection
Cumulative survival
Time(months)
(E)
Log-rank P < .0001
Malignancy
Non-malignancy
70.9%, Non-malignancy
33.3%, Malignancy
Cumulative survival
Time(months)
(F)
Log-rank P = .019
Hypertension
Non-hypertension
71.4%, Non-hypertension
55.8%, Hypertension
Cumulative survival
Time(months)
(G)
Log-rank P = .019
Dysphagia
Non-dysphagia
71.5%, Non-dysphagia
56.1%, Dysphagia
Cumulative survival
Time(months)
(H)
Log-rank P = .001
DM
PM
CADM
86.0%, PM
76.9%, CADM
59.2%, DM
Cumulative survival
Time(months)
(I)
Log-rank P < .0001
Heliotrope rash+
Non-heliotrope rash+
78.8%, Non-heliotrope rash+
52.7%, Heliotrope rash+
Cumulative survival
Time(months)
(J)
Log-rank P = .025
Gottron's papule+
Gottron's papule-
74.9%, Gottron's papule-
61.4%, Gottron's papule+
Cumulative survival
Time(months)

FIGURE 2 Kaplan-Meier survival curves of idiopathic inflammatory myopathy (IIM) patients with different clinical characteristics and subtypes. Survival curves for IIM patients (A) with and without anti-Jo-1 antibody; (B) of different age groups (<60 years and ≥60 years); (C) with and without interstitial lung disease (ILD); (D) with and without pulmonary infection; (E) with and without malignancy; (F) with and without arterial hypertension; (G) with and without dysphagia; (H) having different myositis subsets (DM, dermatomyositis; PM, polymyositis; CADM, clinical amyopathic DM); (I) with and without heliotrope rash; (J) with and without Gottron's papules

TABLE 5 Univariate and multivariate logistic regression analyses of risk factors for ILD in IIM patients

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Gender (F/M)	0.897	0.545-1.476	.669	1.053	0.516-2.147	.887
Age at disease onset						
<30 years	-	-	.004**	-	-	**.004****
30-60 years	6.288	2.339-16.910	<.001***	**12.593**	**2.454-64.631**	**.002****
>60 years	5.000	1.682-14.863	.004**	**21.211**	**3.552-126.653**	**.004****
Fever	1.860	1.137-3.045	.014*	0.799	0.389-1.639	.540
Pulmonary infection	2.156	1.330-3.495	.002**	1.466	0.745-2.884	.268
Myalgia	0.607	0.380-0.970	.037*	1.541	0.782-3.038	.212
Arthralgia	1.626	1.017-2.600	.042*	1.059	0.554-2.024	.863
Heliotrope rash	0.802	0.496-1.297	.368			
Gottron's papule	1.686	1.055-2.695	.029*	**2.342**	**1.112-4.935**	**.025***
V sign	0.566	0.331-0.969	.038*			
Malignancy	0.308	0.099-0.959	.042*	0.386	0.092-1.620	.193
Anti-Ro-52 antibody	3.038	1.841-5.012	<.001***	**2.560**	**1.321-4.964**	**.005****
Anti-Jo-1 antibody	3.556	1.587-7.967	.002***	2.083	0.699-6.208	.188
Albumin	0.895	0.855-0.938	<.001***	**0.915**	**0.857-0.978**	**.009****
Globulin	1.045	1.009-1.083	.014*			
IgG	1.111	1.051-1.174	<.001***			
IgM	1.627	1.132-2.339	.009*	**1.930**	**1.203-3.096**	**.006****
LDH	1.000	0.999-1.000	.499			
ESR	1.009	0.999-1.019	.083			
NLR	0.999	0.969-1.030	.959			
Clinical subsets of IIM						
DM	-	-	.357	-	-	.319
PM	0.802	0.468-1.374	.422	1.165	0.449-3.024	.753
CADM	1.538	0.670-3.529	.310	2.443	0.766-7.795	.131

Abbreviations: CADM, clinical amyopathic dermatomyositis; CI, confidence interval; CK, creatine kinase; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; F/M, female vs. male; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PM, polymyositis.

*$P < .05$.; **$P < .01$.; ***$P < .001$.

According to several recent studies, the incidence rate of myositis-associated malignancy was about 4.25%-17.2%.[32-34] In our patient cohort, the prevalence of malignancy in association with IIM was relatively low (6.3%) compared to reports from other countries.[32-34] The rate we observed could be an underestimation, since patients in our cohort were not systematically screened for this complication. The prevalence of malignancy in our study was similar to a study by Chang et al. which reported a rate of 8.83% among a cohort of 736

TABLE 6 Univariate and multivariate Cox regression analyses of risk factors for death of IIM patients

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Gender (F/M)	0.853	0.528-1.377	.514	0.914	0.525-1.592	.751
Age at disease onset	1.045	1.025-1.065	<.001***	**1.024**	**1.001-1.047**	**.040***
Pulmonary infection	2.450	1.539-3.898	<.001***	1.406	0.802-2.466	.235
ILD	2.218	1.379-3.569	.001**	**2.215**	**1.261-3.891**	**.006****
Dysphagia	1.795	1.088-2.961	.022*	1.358	0.738-2.498	.325
Heliotrope rash	2.410	1.515-3.835	<.001***	1.565	0.889-2.754	.120
Gottron's papules	1.684	1.056-2.684	.029*	1.089	0.616-1.923	.770
Arterial hypertension	1.808	1.089-3.001	.022*	1.206	0.647-2.247	.556
Malignancy	4.083	2.178-7.654	.001**	**3.889**	**1.589-9.517**	**.003****
Anti-Jo-1 antibody	0.200	0.049-0.816	.025*	0.276	0.064-1.190	.084
PLT	0.997	0.994-1.000	.038*	0.999	0.996-1.002	.522
Lymphocyte count	0.509	0.328-0.790	.003**			
NLR	1.037	1.019-1.056	<.001***	**1.029**	**1.004-1.055**	**.025***
Total protein	0.947	0.920-0.974	<.001***			
Albumin	0.897	0.861-0.935	<.001***	**0.933**	**0.881-0.988**	**.018***
AST	1.001	1.000-1.002	.009*	**1.002**	**1.001-1.003**	**.001****
CK	1.000	1.000-1.000	.721			
LDH	1.000	0.999-1.001	.891			
ESR	1.007	0.999-1.016	.091			
Clinical subsets of IIM						
DM	-	-	.002**	-	-	.287
PM	0.273	0.130-0.571	.001**	0.471	0.174-1.279	.140
CADM	0.659	0.284-1.527	.331	1.185	0.469-2.995	.720

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CADM, clinical amyopathic dermatomyositis; CI, confidence interval; CK, creatine kinase; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; F/M, female vs. male; Hb, hemoglobulin; HR, hazard ratio; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; PM, polymyositis.

The variables in bold are those that were statistically significant in the multivariate analysis.

*$P < .05$.; **$P < .01$.; ***$P < .001$.

DM patients (8.83%).[35] Nevertheless, malignancy was the strongest predictor of mortality in our cohort with a HR of 3.889. Malignancy was also the third leading cause of death behind ILD and infection in our cohort. Together, these results indicate that a comprehensive whole-body examination to detect insidious malignancies in patients with IIM should be performed during the early stage of disease.

ILD was identified as a risk predictor for higher mortality of IIM in previous studies,[28,31] which was consistent with findings from our cohort. Similar to other cohorts,[19,28] we found that infection, particularly pulmonary infection, was the predominant cause of death at our center. Indeed, a higher proportion of pulmonary involvements including ILD and infections would increase the risk of respiratory failure despite aggressive treatments, particularly in patients with refractory conditions, such as rapidly progressive ILD (RPILD) with positive anti-MDA5 antibodies. A retrospective study from China focusing on DM/PM patients in the intensive care unit highlighted a substantially poor prognosis of patients with this condition, and noted that the complicated pathogenesis of acute respiratory failure including pulmonary infection and RPILD distinguished IIM as a distinct entity compared with other rheumatic diseases.[36] Our results also revealed that mortality was higher for ILD involving AIP compared to other ILD classifications, although overall there was no difference in clinical features based on radiologic classification of ILD. Therefore, close monitoring and aggressive treatments are

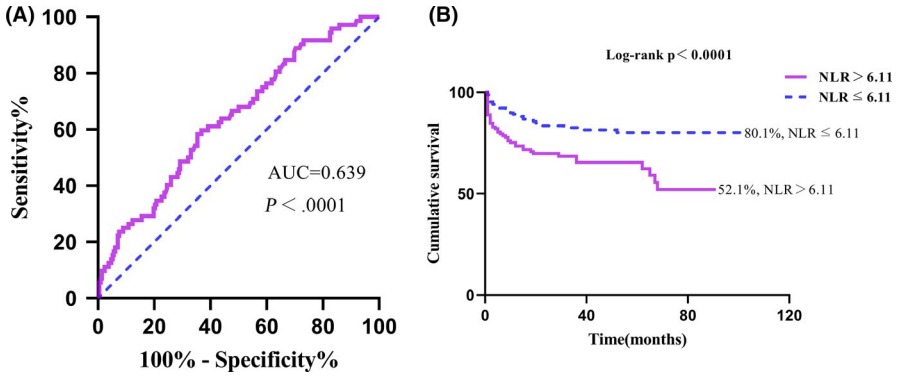

FIGURE 3 (A) Receiver operating characteristic curve for death in idiopathic inflammatory myopathy patients during the follow-up period determined based on NLR; (B) Kaplan-Meier survival curves for patients in the group with NLR ≤6.11 and NLR >6.11. AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio

particularly needed for patients with ILD, especially for those diagnosed with AIP.

Several serum biomarkers such as hypoalbuminemia, NLR and increased levels of AST tended to be associated with poor prognosis in our study, although the relationship was not strong. Our results showed that hypoalbuminemia was independently associated with increased mortality in IIM patients, which was similar to data from other studies.[7,37] As described above, albumin has a number of essential physiological effects for normal health.[23] Persistent inflammation activity and substantial consumption contribute to the increased risk of infections and even malignancy,[35] that can lead to increased mortality. However, the results of continuous data such as serum albumin and AST levels seem to lack substantial clinical implications and may be considered to be less meaningful as they are difficult for clinicians to apply in clinical practice. Therefore, the implications of these findings should warrant attention and be verified by further studies.

NLR has been suggested to be a useful and valuable prognostic biomarker in various disorders, such as cardiovascular and malignant diseases.[38,39] In our study, both univariate and multivariate analyses noted a significant association between NLR and increasing mortality. Thus, we further investigated the predictive value of NLR in the overall survival of IIM patients. In a cohort of 225 PM/DM patients, Ha et al. reported that the optimal threshold for predicting mortality in PM/DM by NLR was 4.775,[7] whereas the cut-off value in our cohort was 6.11. This difference may be caused by different characteristics of the study population and examinations. The Kaplan-Meier curve revealed that mortality of patients with NLR ≥6.11 was significantly higher than that in the control group. Although our data showed that the sensitivity and specificity of NLR for predicting death in IIM patients were comparatively low, measurement of NLR may nonetheless be a useful prognostic biomarker considering its cost-effective value.

Although multivariate analysis did not verify that dysphagia, hypertension, IIM subsets, heliotrope rash and Gottron's papules were independent predictors for mortality in IIM patients, the Kaplan-Meier curve demonstrated that patients with those characteristics did carry a higher risk of death. Several studies noted that dysphagia was an independent predictor of poor prognosis and associated with increased risk for malignancy in IIM patients.[35,40] Dysphagia contributes to an increased risk of infections in IIM patients due to the risk for aspiration and malnutrition. Thus, intensive treatments for patients with dysphagia should be undertaken to increase the quality of life and improve prognosis.

Pairwise comparisons showed a significant difference in mortality between DM and PM subgroups, although no such difference was seen between DM and CADM subsets. A Chi-square test indicated that the proportion of patients in the DM group with baseline NLR ≥6.11 was significantly higher than that in the other 2 groups (46.7% vs. 31.6% for DM vs. PM and 46.7% vs. 30.8% for DM vs. CADM, P =.042). Additionally, the percentage of DM patients who died from infections appeared to be higher than that for the other groups (51.7% vs. 44.4% for DM vs. PM and 51.7% vs. 33.3% for DM vs. CADM). A potential reason for higher risk of death in DM patients may be that these patients have a higher risk of infection compared to PM and CADM patients. The 5-year survival rates in the DM group were significantly lower than that for the PM patients (65.2% vs 90.0%, P < .001), which was similar to results from other cohorts.[2,3,29,41] An earlier study involving a cohort of Swedish patients also indicated that the survival curve descended most rapidly within 1 year of diagnosis.[3] Therefore, careful monitoring and aggressive interventions, particularly for DM patients, are needed during the early stage of disease.

Glucocorticoids (GCs) remain a mainstay for treatment of IIM. However, the infection risk secondary to high-dose GC therapy for primary disease warrants additional attention. Our study suggested that patients treated with methylprednisolone pulse therapy had a higher mortality rate than the controlled for ILD group and there were no significant differences in radiologic classifications of ILD between the 2 groups. Thus, we speculated that the higher mortality rate in patients treated with methylprednisolone pulse was not only related to disease severity, but also to the increased risk of infection secondary to intensive immunosuppressive therapy. Several retrospective studies demonstrated that application of GCs and/or immunosuppressive agents were risk factors for infection in IIM patients.[16,19,42] These results underscore that the need for comprehensive consideration of precautions to prevent secondary infections and the need to control primary disease should be taken into account for clinicians before using high-dose GCs, especially when treating IIM patients with ILD. Further randomized controlled trials

are needed to clarify the efficacy of glucocorticoids in management of IIM.

Our study had several limitations. Due to the retrospective nature of the study, information bias and recall bias were inevitably present. Further, treatment modalities of the entire follow-up periods were not obtained due to the retrospective analysis such that evaluation of the impact of therapies on prognosis was not possible. Data on myositis autoantibody profiles were not available since examinations of microaggregates of albumin were not widely performed until 2018. Last, there was some truncated data in survival analysis and the survival outcomes for several patients needed to be further tracked. Thus, calculating the median survival time of patients was difficult. Future prospective and multicenter studies in which patients are grouped according to the subsets of myositis autoantibody, such as anti-MDA5 antibody, are needed to determine the risk factors associated with ILD and mortality in IIM patients.

5 | CONCLUSION

In summary, this retrospective study enhanced our understanding of the features of IIM-associated ILD and identified patients having high risk for mortality based on clinical characteristics. Age at onset, Gottron's papules, anti-Ro-52 antibodies and elevated serum IgM, as well as hypoalbuminemia were identified as risk factors for IIM-associated ILD. Furthermore, we confirmed age at onset, ILD, malignancy, elevated serum AST and NLR and hypoalbuminemia as predictors for higher mortality in IIM patients. These findings highlight that close surveillance and aggressive treatments may be required for IIM patients having unfavorable predictive factors, especially patients with ILD and malignancy. For future studies, our study might be helpful to provide longitudinal information on the outcome of IIM patients, as well as survival and mortality rates.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, to the interpretation of the results and to the writing of the manuscript. Lingli Dong mainly contributed to the conception and design. Zhiqian Bai analyzed the data and wrote the first draft of the manuscript. Guifen Shen critically revised the article for important intellectual content. All authors read, commented upon and edited various drafts and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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