Pleural effusion as a predictor of rapidly progressive interstitial lung disease and mortality in idiopathic inflammatory myopathies

X. Liang[1], H. Ren[2], F. Xiao[1], S. Zheng[1], R. Wang[1], C. Huang[1], J. Guo[1], J. Li[1,3], J. Zhu[1]

[1]Department of Rheumatology and Immunology, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Southern Medical University, Guangzhou, China; [3]Department of Traditional Chinese Internal Medicine, School of Traditional Chinese Medicine, Southern Medical University, Guangzhou, China.

Abstract

Objective

This study aimed to evaluate the clinical significance of pleural effusion in adult patients with idiopathic inflammatory myopathies (IIM).

Methods

We assessed a cohort of 158 consecutive patients with IIM. Clinical features and survival rates were compared between patients with and without pleural effusion.

Results

Of those 158 IIM patients, 28 (17.7%) developed pleural effusion. 125 (79.1%) IIM patients had interstitial lung disease (ILD), 26 (20.8%) of which developed pleural effusion. Notably, pleural effusion was associated with a higher incidence of lower lung zone consolidation, rapidly progressive ILD (RP-ILD) and elevated high-resolution computed tomography (HRCT) score, and could robustly predict RP-ILD independently [HR 7.863 (2.160-28.617), p=0.002] in IIM-ILD patients. IIM patients with pleural effusion presented with increased systemic inflammatory response, including more fever, elevated white blood cell count, neutrophil/lymphocyte ratio, C-reactive protein, and erythrocyte sedimentation rate, alongside reduced lymphocyte percentage. Pleural effusion was also associated with more ILD, lower lung zone consolidation, pericardial effusion and RP-ILD, higher HRCT score, and lower HB and albumin levels in IIM. Except for neutrophil/lymphocyte ratio, ILD and pericardial effusion, other correlative variables were potential predictors of higher mortality in IIM. Furthermore, pleural effusion remained an independent predictor of higher mortality in IIM [HR 5.05 (1.633-15.62), p=0.005].

Conclusion

Pleural effusion showed a significant positive association with severe phenotypes of ILD and was the powerful predictor of RP-ILD in IIM-ILD. Furthermore, pleural effusion could reveal adverse disease phenotypes with higher systemic inflammatory level and predict higher mortality independently in IIM.

Key words

idiopathic inflammatory myopathies, pleural effusion, interstitial lung disease, mortality

*Xiao Liang, MS**
*Huaming Ren, BS**
Fei Xiao, MS
Songyuan Zheng, MS
Ran Wang, PhD
Chuping Huang, MS
Jinger Guo, MS
Juan Li, PhD,
Junqing Zhu, PhD

**Contributed equally.*

Please address correspondence to:
Junqing Zhu
Department of Rheumatology and Immunology,
Nanfang Hospital,
Southern Medical University,
1838 North of Guangzhou Avenue,
510510 Guangzhou, Guangdong, China.
E-mail: jqzhujq@yeah.net

and to:
Juan Li
E-mail: lijuan@smu.edu.cn

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Introduction

Idiopathic inflammatory myopathies (IIM) are a group of autoimmune disorders affecting the skeletal muscles and a variety of organs. Interstitial lung disease (ILD) is the primary cause of morbidity and mortality in IIM, especially rapidly progressive ILD (RP-ILD) with a high mortality rate (1, 2). Pleural effusion is fluid accumulation in the pleural cavity arising from various aetiological factors, generally indicating an underlying pathology (3). Systemic autoimmune diseases can affect the pleura, causing pleural effusion and chest pain with varying frequencies and manifestations (4, 5). Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) frequently present with pleural effusion, ranging from 5–20% and 17-60% of cases, respectively (6). The role of autoimmunity associated with underlying ILD and Connective tissue disease (CTD) itself has been postulated as an important cause of pleural effusion in IIM (7). Pleural effusion occurs in patients with various forms of ILD (8). However, by contrast to the frequent ILD involvement, the development of pleural effusion has not gained enough attention in individuals with IIM before, despite pleural irregularities being frequently seen on high-resolution computed tomography (HRCT) scan (7, 9). Upon reviewing the available literature, 12 cases of significant pleural effusion had been reported in IIM, and ILD complicated 66.7% of these patients (7, 10-20). Besides these case reports, pleural effusion was documented in minority of observational studies for IIM-associated ILD. Fujisawa *et al*. noted pleural effusion in 9 of 102 patients (8.8%) with IIM-ILD (21). In a series of IIM-ILD, the prevalence of pleural effusion was estimated as 5% (22). However, owing to the fact that such studies regarding pleural effusion as a variable were scarce and lacking HRCT scans, the gold standard in detecting pleural fluid (23), the prevalence of pleural effusion was largely unknown until now. And there have been no prior studies that have evaluated the association between pleural effusion and the severity and progression of ILD in IIM.

The prognostic value of pleural effusion in IIM is still unclear as well (6). According to Fujisawa's study, pleural effusion was not linked to the prognosis for IIM-ILD patients (21). Most of the 12 reported cases of IIM patients with overt pleural effusion responded well to immunosuppressive therapy and survived (7, 10-20). Whereas, some of the former case reports suggested that pleural effusion could worsen the prognosis of IIM patients and exacerbate their condition (11, 17). Broadly speaking, due to few reported studies regarding this topic, the prognosis of IIM patients with pleural effusion remains unknown.

This investigation aimed to explore the association between pleural effusion and the severity and progression of ILD in IIM-ILD patients and to unravel the impact of pleural effusion on the prognosis of IIM.

Materials and methods

Study population and design

In this retrospective cohort study conducted at Nanfang Hospital, medical records of 158 consecutive patients diagnosed with IIM were reviewed. The study spanned from December 2015 to June 2022, during which patients were screened for myositis-specific antibodies (MSAs) and myositis-associated autoantibodies (MAAs) utilising a commercial immunoblot assay capable of testing for 16 autoantigens. The diagnostic criteria for polymyositis (PM) were based on either the Bohan and Peter criteria or the EULAR/ACR 2017 classification criteria (24, 25). The classification of dermatomyositis (DM) and clinically amyopathic DM (CADM) were established using the 239 ENMC International Symposium: Amsterdam Classification of Dermatomyositis (26). The diagnosis of immune-mediated necrotising myopathy (IMNM) was based on the 224 ENMC International Symposium: clinical seropathological classification of immune-mediated necrotising myopathies (27). Antisynthetase antibody syndrome (ASS) was diagnosed with the criteria proposed by Solomon *et al*. (28). Eligibility for the study was set at an age threshold of 18 years or above. Exclusions were made

for individuals presenting with tumours, pulmonary infections, or other specified CTDs. A comprehensive data set including demographics, clinical manifestations, laboratory results, and administered treatment regimens at hospital admission was compiled from the medical records of the patients. Follow-up data collection extended up to January 2023, facilitating the assessment of cumulative survival rates. The study complies with the Helsinki Declaration and was approved by the Ethics Committee Board of Nanfang Hospital, Southern Medical University (NFEC2022378). Written informed consent was not required owing to the retrospective observational nature of the study.

Detection of pleural effusion

The chest radiograph (CXR), chest HRCT scan, and thoracic ultrasonography were reviewed by our team for the presence of pleural effusion according to British Thoracic Society pleural disease guideline (29). If there were any inconsistencies among the above examination methods, HRCT scan would be used as the final criterion for the presence of pleural effusion as it is the gold standard with superior sensitivity in detecting fluid in the pleural space (3, 23).

Diagnosis and assessment of ILD

The diagnosis of ILD was confirmed through HRCT scan. Two radiologists, blinded to the clinical data of the patients, independently reviewed the HRCT images. Within a three-month span post the initial ILD diagnosis, patients exhibiting an acute and progressive worsening of dyspnoea due to ILD, necessitating hospital admission, additional oxygen, or intubation, were identified as having RP-ILD (30). Adhering to the guidelines set forth by the American Thoracic Society and the European Respiratory Society, the HRCT images were systematically categorised into 3 distinct morphological patterns of ILD: non-specific interstitial pneumonia (NSIP), organising pneumonia (OP), and NSIP combined with OP. Lower lung zone consolidation was characterised by a uniform elevation in opacity of the pulmonary parenchyma, leading to the obscuration of vascular and airway wall boundaries and the lesions distributed beneath the inferior pulmonary vein (31). HRCT imaging score was evaluated based on the classification by Ichikado *et al*. (32, 33): the HRCT score was determined using a scale ranging from 1 to 6 in all instances. The lungs were divided into 6 zones (upper, middle, and lower on both sides). The extent of each abnormality was assessed by visually evaluating the proportion (rounded to the nearest 5%) of lung parenchyma affected in each zone. The aggregate score for each patient was computed by taking the mean of the score across the six zones.

Statistical analysis

Categorical variables across groups were compared using either the chi-squared test or Fisher's exact test. Continuous data were analysed with either Student's t-test or Mann-Whitney U-test, contingent on the data's distribution. Survival analysis was performed using the Kaplan-Meier method with the log-rank test. A univariate Cox regression was undertaken to ascertain relationships between variables and clinically important outcomes; variables with a significance level of $p<0.5$ in this analysis were considered as potential predictors. Subsequently, the least absolute shrinkage and selection operator for Cox regression (LASSO-Cox) coordinated with the Akaike information criterion (AIC) techniques were applied to select the optimal multivariate Cox proportional hazards model. Analytical procedures were executed employing the SPSS software (v. 26.0; IBM Corp, Armonk, NY) and the R statistical environment (v. 4.2.3; R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). A 2-tailed p-value threshold of <0.05 was established for statistical significance.

Results

Clinical features among IIM patients with and without pleural effusion

Clinical features of 158 enrolled patients with IIM are summarised in Table I. Mean age at diagnosis was 47.04 years (S.D. 13.00), and 61.4% (97/158) were female. Among these participants, 17.7% (28/158) had pleural effusion. No patients with IMNM developed pleural effusion. Notably, there were 2 or more MSAs detected in some individuals, leading to the totality of MSAs subtypes exceeding the number of patients with positive MSAs. In patients with IIM, pleural effusion was associated with increased likelihood of pericardial effusion ($p<0.001$), and lower albumin ($p<0.001$), lower haemoglobin (HB) level ($p=0.015$), as well as a higher prevalence of not having been exposed to any immunosuppressant ($p=0.006$) and of having received intravenous immunoglobulin (IVIG) ($p=0.005$), and lower prevalence of having received 2 or more immunosuppressants ($p=0.036$). Additionally, this group had more fever ($p=0.001$), higher white blood cell count (WBC) level ($p=0.003$), higher erythrocyte sedimentation rate (ESR) ($p=0.003$), higher C-reactive protein (CRP) ($p<0.001$), and higher neutrophil/lymphocyte ratio (NLR) ($p<0.001$), as well as lower percentage of lymphocyte (LY%) ($p=0.002$) than IIM patients without pleural effusion, all of which could indicate a higher level of systemic inflammation (33, 34).

In the ILD domain, we noticed significant heterogeneity in IIM patients with and without pleural effusion. It was discovered that patients with pleural effusion had a higher occurrence of ILD ($p=0.049$), RP-ILD ($p=0.005$) and lower lung zone consolidation ($p=0.017$), and higher HRCT score ($p<0.001$) than those without pleural effusion.

Correlation between pleural effusion and the severity and progression of ILD in IIM-ILD patients

To explore the impact of pleural effusion on ILD, we excluded IIM patients without ILD, leaving us with a cohort of IIM-ILD patients. There were 125 (79.1%) IIM-ILD patients in our cohort, 26 patients (20.8%) of whom had pleural effusion. We found that there was a higher prevalence of lower lung zone consolidation ($p=0.047$), RP-ILD ($p=0.013$), and higher HRCT score ($p<0.001$) in IIM-ILD patients with pleural effusion compared to those without pleural effusion (Supplementary Table S1). Besides, IIM-ILD patients with pleural

Table I. Comparison of clinical features between IIM patients with and without pleural effusion.

Characteristic	Total n=158)	Without pleural effusion (n=130)	With pleural effusion (n=28)	*p*-value
Demographics				
Follow-up time, (median [IQR])	24.50 [14.25, 48.00]	25.00 [16.25, 48.00]	16.00 [4.75, 41.00]	0.036
Age, years, mean (S.D.)	47.04 (13.00)	46.11 (12.90)	51.39 (12.78)	0.051
Female gender, n (%)	97 (61.4)	79 (60.8)	18 (64.3)	0.832
Smoking, n (%)	28 (17.7)	23 (17.7)	5 (17.9)	1.000
Diagnosis				
DM, n (%)	49 (31.0)	39 (30.0)	10 (35.7)	0.553
PM, n (%)	7 (4.4)	5 (3.8)	2 (7.1)	0.608
CADM, n (%)	26 (16.5)	21 (16.2)	5 (17.9)	0.784
ASS, n (%)	48 (30.4)	37 (28.5)	11 (39.3)	0.259
IMNM, n (%)	28 (17.7)	28 (21.5)	0 (0.0)	**0.005**
Clinical manifestations				
Fever at presentation, n (%)	37 (23.4)	23 (17.7)	14 (50.0)	**0.001**
Rash, n (%)	103 (65.2)	83 (63.8)	20 (71.4)	0.517
Heliotrope rash, n (%)	66 (41.8)	52 (40.0)	14 (50.0)	0.399
Gottron papule/sign, n (%)	73 (46.2)	62 (47.7)	11 (39.3)	0.532
V-neck sign, n (%)	50 (31.6)	39 (30.0)	11 (39.3)	0.374
Periungual erythema, n (%)	23 (14.6)	21 (16.2)	2 (7.1)	0.374
Skin ulcers, n (%)	38 (24.1)	34 (26.2)	4 (14.3)	0.228
Mechanic's hands, n (%)	49 (31.0)	42 (32.3)	7 (25.0)	0.507
Raynaud phenomenon, n (%)	26 (16.5)	20 (15.4)	6 (21.4)	0.411
Dysphagia, n (%)	35 (22.2)	26 (20.0)	9 (32.1)	0.208
Hoarseness, n (%)	18 (11.4)	15 (11.5)	3 (10.7)	1.000
Peripheral edema, n (%)	29 (18.4)	21 (16.2)	8 (28.6)	0.175
Articular symptom, n (%)	86 (54.4)	74 (56.9)	12 (42.9)	0.211
Cardiovascular involvement, n (%)	17 (10.8)	11 (8.5)	6 (21.4)	0.084
Pulmonary hypertension, n (%)	20 (12.7)	14 (10.8)	6 (21.4)	0.128
Muscle involvement, n (%)	115 (72.8)	96 (73.8)	19 (67.9)	0.494
Pericardial effusion, n (%)	22 (13.9)	11 (8.5)	11 (39.3)	**<0.001**
ILD domain				
ILD, n (%)	125 (79.1)	99 (76.2)	26 (92.9)	**0.049**
HRCT score, (median [IQR])	112.99 [104.34, 136.97]	108.87 [104.06, 126.41]	145.57 [125.22, 185.17]	**<0.001**
RP-ILD, n (%)	18 (11.4)	10 (7.7)	8 (28.6)	**0.005**
Lower lung zone consolidation, n (%)	42 (26.6)	29 (22.3)	13 (46.4)	**0.017**
HRCT patterns, n (%)				0.400
NSIP	36 (28.8)	31 (23.9)	5 (17.9)	0.493
OP	48 (38.4)	38 (29.2)	10 (35.7)	0.499
NSIP combine OP	41 (32.8)	30 (23.1)	11 (39.3)	0.076
Laboratory features				
WBC, mean (S.D.)	7.06 (3.19)	6.71 (3.01)	8.65 (3.59)	**0.003**
HB, mean (S.D.)	125.93 (17.28)	127.48 (15.45)	118.75 (23.05)	**0.015**
LY%, mean (S.D.)	21.64 (11.47)	22.95 (11.43)	15.60 (9.72)	**0.002**
NLR, (median [IQR])	3.63 [2.31, 5.57]	3.37 [2.16, 4.95]	5.10 [3.89, 8.96]	**<0.001**
ESR, mm/h, (median [IQR])	24.00 [12.00, 40.75]	23.00 [11.00, 34.87]	43.00 [19.00, 68.67]	**0.003**
CRP, mg/L, (median [IQR])	4.75 [1.91, 13.24]	4.33 [1.37, 8.26]	21.67 [11.26, 45.15]	**<0.001**
CK level, U/L, (median [IQR])	253.50 [72.25, 2447.61]	332.00 [69.75, 2674.50]	136.00 [84.50, 2149.00]	0.982
LDH, U/L, (median [IQR])	360.50 [243.50, 575.75]	348.66 [240.25, 563.00]	474.00 [296.00, 724.25]	0.092
ALT, U/L, (median [IQR])	49.00 [20.00, 105.75]	49.00 [20.00, 104.50]	48.50 [24.75, 114.92]	0.612
AST, U/L, (median [IQR])	56.00 [24.25, 129.50]	51.00 [24.00, 123.75]	74.50 [29.00, 175.71]	0.158
Albumin, g/L, mean (S.D.)	35.44 (5.17)	36.37 (4.72)	31.14 (5.07)	**<0.001**
ANA (≥1:80), n (%)	91 (57.6)	72 (55.4)	19 (67.9)	0.293
MSAs positive, n (%)	147 (93.0)	123 (94.6)	24 (85.7)	0.107
Subtypes of MSAs, n (%)				
Anti-MDA5	50 (31.6)	42 (32.3)	8 (28.6)	0.824
Anti-Mi2	17 (10.8)	12 (9.2)	5 (17.9)	0.187
Anti-TIF-γ	8 (5.1)	6 (4.6)	2 (7.1)	0.632
Anti-NXP2	13 (8.2)	12 (9.2)	1 (3.6)	0.467
Anti-Jo1	27 (17.1)	21 (16.2)	6 (21.4)	0.580
Anti-PL7	15 (9.5)	13 (10.0)	2 (7.1)	1.000
Anti-PL12	7 (4.4)	6 (4.6)	1 (3.6)	1.000
Anti-EJ	9 (5.7)	8 (6.2)	1 (3.6)	1.000
Anti-OJ	7 (4.4)	5 (3.8)	2 (7.1)	0.608
Anti-SAE	2 (1.3)	2 (1.5)	0 (0.0)	1.000
Anti-SRP	23 (14.6)	22 (16.9)	1 (3.6)	0.080
Anti-HMGCR	15 (9.5)	15 (11.5)	0 (0.0)	0.075
Therapies				
Exposure to high-dose glucocorticoid (>80 mg), n (%)	68 (43.0)	53 (40.8)	15 (53.6)	0.293
No. of immunosuppressants, on top of steroid, n (%)				**0.010**
0	32 (20.3)	21 (16.2)	11 (39.3)	**0.006**
1	84 (53.2)	70 (53.8)	14 (50.0)	0.711
>=2	42 (26.6)	39 (30.0)	3 (10.7)	**0.036**
IVIg, n (%)	43 (27.2)	29 (22.3)	14 (50.0)	**0.005**
Exposure to pirfenidone, n (%)	24 (15.2)	18 (13.8)	6 (21.4)	0.382

DM: dermatomyositis; IMNM: immune-mediated necrotising myopathy; PM: polymyositis; CADM: clinically amyopathic dermatomyositis; ASS: antisynthetase syndrome; MSAs: myositis-specific autoantibodies; MDA5: melanoma differentiation-associated gene 5; TIF1-γ: transcriptional intermediary factor 1 gamma; SAE: small ubiquitin-like modifier activating enzyme; NXP2: nuclear matrix protein 2; Jo-1: histidyl-tRNA-synthetase; PL-12: alanyl-tRNA synthetase; PL-7: threonyl-tRNA synthetase; EJ: glycyl-tRNA synthetase; OJ: isoleucyl-tRNA synthetase; HMGCR:3-hydroxy-3-methylglutaryl-coenzyme A reductase; SRP: signal recognition particle; ILD: interstitial lung disease; RP-ILD: rapidly progressive interstitial lung disease; HRCT: high-resolution computed tomography. NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; WBC: white blood cell count; HB: haemoglobin; LY%: percentage of lymphocyte; NLR: neutrophil/lymphocyte ratio; CK: creatine kinase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANA: anti-nuclear antibody; IVIG: intravenous immunoglobulin. Bold indicates statistical significance.

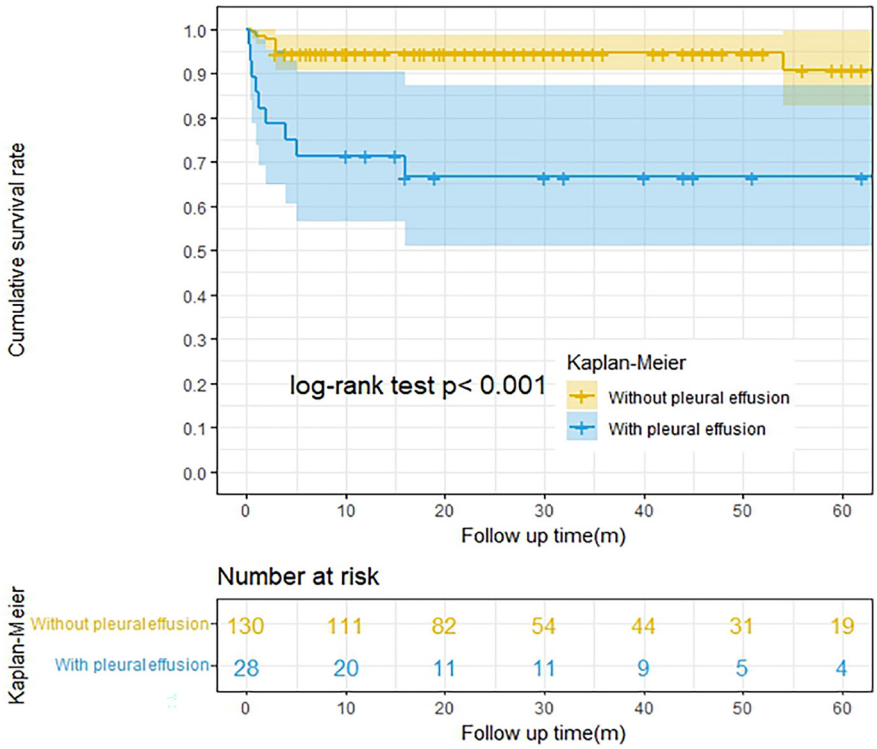

Fig. 1. Kaplan-Meier survival curves of RP-ILD in IIM-ILD patients with and without pleural effusion. The cumulative RP-ILD rate was significantly higher in IIM-ILD patients with pleural effusion than those without pleural effusion (30.8% *vs*. 10.1%; p=0.003). RP-ILD: rapidly progressive interstitial lung disease.

Table II. Results of multivariable Cox regression analysis for RP-ILD in IIM-ILD patients.

Variable	Hazard ratio	HR (95% CI)	p-value
Anti-MDA5	18.830	4.616-76.817	**0.000**
Muscle involvement	0.146	0.044-0.486	**0.002**
Albumin	0.822	0.734-0.920	**0.001**
Pleural effusion	7.863	2.160-28.617	**0.002**

Bold indicates statistical significance.
MDA5: melanoma differentiation-associated gene 5.

effusion also had more fever (p=0.005), higher WBC level (p=0.013), higher ESR (p=0.025), higher CRP (p<0.001), and higher NLR (p=0.008), as well as lower LY% (p=0.024).

RP-ILD was the major cause of death, accounting for 66.7% of non-survivors in IIM-ILD patients. As shown in the Kaplan-Meier survival curves, a significantly higher proportion of RP-ILD was observed in IIM-ILD patients with pleural effusion than those without pleural effusion (p=0.003) (Fig. 1). Clinical features of IIM-ILD patients with RP-ILD and predictors of RP-ILD in the univariate Cox regression analysis are summarised in Supplementary Table S2. Both lower lung zone consolidation (p=0.028) and higher HRCT score (p=0.015) were potential predictors of RP-ILD in IIM-ILD patients. 16 potential predictors (p<0.05) of RP-ILD were reduced to 6 most valuable variables in the LASSO Cox regression in Supplementary Fig. S1. Then, in the backward stepwise selection algorithm, we identified the optimal multivariable Cox regression model with the lowest AIC value, which included 4 variables, as shown in Table II. In the final multivariable Cox regression analysis, pleural effusion was the independent predictor of RP-ILD [HR 7.863 (2.160-28.617), p=0.002] after adjusting for other covariates.

As pleural effusion was tightly linked with RP-ILD, we next explored whether RP-ILD correlated with prognosis. The cumulative survival rate for patients with IIM-ILD but without RP-ILD was 94.4%, while the rate of patients with IIM-ILD and RP-ILD was only 33.3 % (p<0.001) (Suppl. Fig. S2).

Mortality data in IIM patients with and without pleural effusion

Overall, 11.4% (18/158) of IIM patients died, including 6.2% (8/130) of patients without pleural effusion and 35.7% (10/28) of those with pleural effusion. Patients with pleural effusion had a significantly worse unadjusted cumulative survival than those without pleural effusion (p<0.001, log-rank test) (Fig. 2). RP-ILD accounted for 70% (7/10) of non-survivors with pleural effusion and 62.5% (5/8) of deaths without pleural effusion. Among IIM patients who died, the median time to death from diagnosis was significantly shorter in patients with pleural effusion when compared with patients without pleural effusion [1.60 months (IQR 0.48–7.75) *vs*. 3.0 months (IQR 1.25–3.00)].

The prognostic significance of pleural effusion in IIM patients

Given the significantly lower survival rate observed in IIM patients with pleural effusion compared to those without, we aimed to investigate whether pleural effusion was an independent predictor of prognosis in IIM. Clinical features of IIM patients with non-survivors and predictors of mortality are summarised in Supplementary Table S3. Based on the results of the univariate Cox regression analysis, higher ESR (p=0.038), higher CRP (p=0.031), higher HRCT score (p=0.022), fever (p=0.003), pleural effusion (p<0.001), rash (p=0.020), skin ulcers (p=0.003), cardiovascular involvement (p= 0.020), anti-MDA5 antibody (p=0.003), lower lung zone consolidation (p=0.013), and RP-ILD (p<0.001) were discovered to be potential predictors of mortality. Meanwhile, higher HB (p<0.001) and higher albumin levels (p<0.001) were found to be protective factors against mortality.

13 candidate predictors with p<0.5 in the univariate analysis were reduced to 4 most valuable variables using LASSO Cox regression in Supplementary Fig. S3. The final multivariable Cox re-

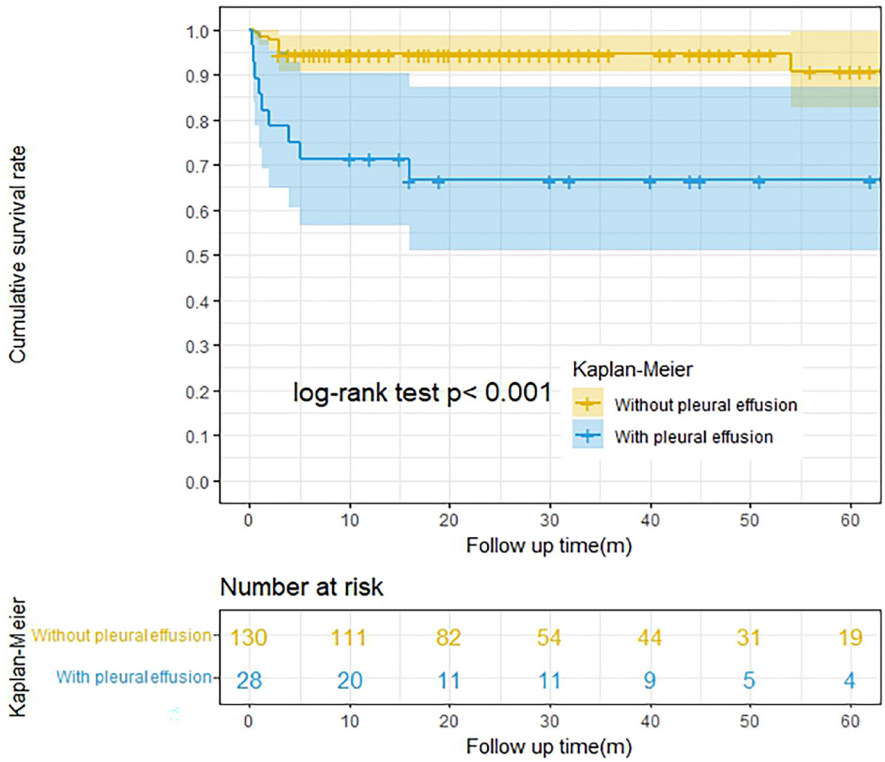

Fig. 2. Kaplan-Meier survival curves of mortality in IIM patients with and without pleural effusion. The cumulative survival rate was significantly lower in IIM patients with pleural effusion than those without pleural effusion (64.3% *vs*. 93.8%; $p<0.001$).

Table III. Results of multivariable Cox regression analysis for mortality in IIM patients.

Variables	Hazard ratio	HR (95% CI)	*p*-value
Albumin	0.846	0.750-0.954	**0.006**
RP-ILD	20.919	5.853-74.758	**0.000**
Pleural effusion	5.050	1.633-15.620	**0.005**
Skin ulcers	3.504	0.967-12.696	0.056

Bold indicates statistical significance.
RP-ILD: rapidly progressive interstitial lung disease.

gression model, including 4 variables, with the lowest AIC value indicated: that pleural effusion was the independent predictor of higher mortality [HR 5.050 (1.633-15.620), p=0.005] after adjusting for other covariates, as shown in Table III. RP-ILD [20.919 (5.853-74.758), p=0.000] was also an independent predictor of higher mortality. A higher albumin level [0.846 (0.750-0.954), p=0.006] was an independent protective factor for reduced mortality.

Discussion

In the present study, pleural effusion showed a significant positive association with severe ILD phenotypes and was the potent predictor for RP-ILD in IIM-ILD. Meanwhile, pleural effusion was correlated with unfavourable disease phenotypes including enhanced systemic inflammatory response and could predict higher risk of mortality independently in IIM.

Previously, very few observational studies had focused on IIM patients with pleural effusion and described the incidence rate of pleural effusion, making it hard to evaluate the prevalence of pleural effusion. The others were limited case reports, providing details on the clinical characteristics and outcomes of IIM patients with pleural effusion. In our cohort, we found that up to 17.7% of IIM patients had pleural effusion, most of which coexisted with ILD. In a series of 28 IIM-ILD patients the prevalence of pleural effusion was estimated as 5% (22) and in a cohort of 102 IIM-ILD patients the prevalence was 8.8% (21). The higher prevalence of pleural effusion in our cohort is likely due to population and regional differences. Previous reports suggested that autoimmunity associated with underlying IIM was potentially an important cause of pleural effusion (35). However, there are various potential causes for pleural effusion, mainly including pulmonary infections, congestive heart failure, and malignancy, making it difficult to determine the aetiology (3, 7). To avoid potential interference to the maximum, patients with pulmonary infections or malignancies were excluded from our study. According to previous reports, the frequency of cardiovascular involvement in patients with IIM spanned from 9% to 72% (36). Thus, we did not rule out the patients with cardiac dysfunction. The above measures made it possible that the development of pleural effusion in our IIM cohort was contributed by immune injury. It was reported that there could be an association between pleural effusion and CTD-ILD (8). In a large cohort of SLE, a significant association of ILD with serositis, which included pleural effusion and/or pericardial effusion, was found (37).Prospective studies using HRCT demonstrate that up to 20% of patients with rheumatoid pleural effusion have associated HRCT evidence of fibrosing alveolitis (38). However, it remains unknown about the relationship between pleural effusion and the severity and progression of ILD in IIM populations. In our present cohort, 92.9% (26/28) of IIM patients with pleural effusion developed ILD, whose prevalence was significantly higher than those without pleural effusion. After excluding patients without ILD, a higher incidence of lower lung zone consolidation, RP-ILD and higher HRCT score were observed in IIM-ILD patients with pleural effusion than those without. We found that RP-ILD was significantly associated with poor prognosis in IIM-ILD patients. Lower lung zone consolidation and higher HRCT score were potential predictors of RP-ILD. Corresponding to previous studies, these three variables related to

ILD could represent severe ILD phenotypes, and their association with poor prognosis is notable (31, 39). Furthermore, our study showed that pleural effusion could robustly and independently predict the development of RP-ILD in IIM-ILD patients. Above all, we concluded that pleural effusion was associated with severe ILD phenotypes and could powerfully predict RP-ILD in IIM-ILD.

The prognosis of IIM patients with pleural effusion is still being determined, mainly due to the limited reports available on this topic. Fujisawa's study found no association between pleural effusion and the prognosis of IIM-ILD patients (21). Out of 12 published cases of IIM patients with pleural effusion, 10 (83.3%) recovered, and 2 (16.7%) failed intensive treatment and died of respiratory failure (7, 10-20). Of the 2 patients who died, one continued to exhibit substantial pleural effusion, and pleural effusion resolved in the other patient (12, 17). Our study demonstrated that IIM patients with pleural effusion had a significantly higher mortality rate than those without, and pleural effusion was the independent predictor of higher mortality in IIM. A higher incidence of fever, and increased WBC, NLR, CRP, and ESR levels, alongside diminished LY% were observed in IIM patients with pleural effusion than those without, implying the increased systemic inflammatory response and immune-cell hyperactivation that can be triggered by autoimmune conditions (33, 34). In our study, it was also found that IIM patients with pleural effusion were correlated with a higher incidence of pericardial effusion, ILD, lower lung zone consolidation, RP-ILD, higher HRCT score and lower albumin level. Interestingly, except for NLR, ILD and pericardial effusion, other correlative variables were potential predictors of higher mortality; moreover, RP-ILD and lower albumin level were independent predictors of higher mortality in IIM. These findings suggest that pleural effusion is associated with more serious disease phenotypes and worse prognosis in IIM. RP-ILD has gained significant attention in IIM owing to its exceedingly poor prognosis (40), which is consistent with our study. Among IIM patients in our cohort, RP-ILD had a mortality rate of 66.7%. We suggested that the more severe phenotypes of ILD, especially markedly higher occurrence of RP-ILD, could account for a worse prognosis for IIM patients with pleural effusion than those without. In recent years, studies have been increasingly searching for prognostic markers to stratify IIM patients and manage them appropriately (41). Our study added that pleural effusion could serve as a robust indicator for worse prognosis in IIM. To our best knowledge, this is the first study showing the value of pleural effusion in predicting the outcomes of IIM.

Several mechanisms may be involved in the association between pleural effusion and the severity and progression of ILD in IIM-ILD patients. Firstly, previous studies have suggested that pleural involvement in IIM patients is probably caused by immune pleuritis associated with underlying ILD (6, 7). It has been suggested that the pathogenesis of pleural effusion could be due to complement activation within the pleural microvasculature (12). Vascular injury, probably resulting from inappropriate complement activation, is central to DM and linked to PM and inclusion-body myositis (IBM) (42). Formation of membrane attack complexes deposited on the endothelial cell, resulting in endothelial injury, is responsible for pulmonary lesions associated with this disease (43). Accordingly, we postulate that complement activation and consequent vasculopathy may be the shared aetiologies of pleural effusion and ILD in IIM. Secondly, systemic inflammatory diseases, a category inclusive of various autoimmune disorders, could impact the pleura, resulting in pleural effusion (6). Elevated systemic inflammatory response, such as activation of interferon (IFN) pathways and activated macrophages, plays a crucial role in IIM-ILD, especially in patients with severe ILD, such as in anti-MDA5-associated ILD (43). Some studies suggested that enhanced systemic inflammatory state could drive progressive pulmonary fibrosis (44, 45). The significantly different inflammatory indicators which signify the higher systemic inflammatory level, combined with severe ILD phenotypes and more RP-ILD seen in IIM-ILD patients with pleural effusion, were in line with aforementioned mechanisms. Lastly, in severe ILD, hyperactivated inflammation can cause markedly increased capillary permeability, increasing the rate of pleural fluid accumulation (46, 47). Meanwhile, disseminated inflammation of the lung interstitium in severe ILD could also potentially extend to affect the pleura, leading to pleural effusion (8). Schwarz *et al*. presented histologic changes of pleural inflammation involved in 50% of their 6 IIM-ILD patients (48). To summarise, these mechanisms provide support for the positive association of pleural effusion with severe phenotypes of ILD and RP-ILD in IIM-ILD.

This study presents noteworthy clinical significance regarding pleural effusion. Nevertheless, there are certain limitations of this investigation that deserve to be mentioned. First, this study was conducted retrospectively at a single institution, which had several inevitable limitations, including selection bias, reporting bias, and information bias. Second, owing to the lack of chest ultrasonography in most patients, the quantification of pleural effusion in IIM patients was not done in our study, which may have an important clinical meaning in IIM. Finally, another drawback was the absence of pulmonary function testing owing to the serious pulmonary condition in some IIM patients, which is an important tool for the evaluation of ILD.

In conclusion, this is the first study evaluating the predictive value of pleural effusion in IIM outcomes. This study unveiled a strong link between pleural effusion and severe phenotypes of ILD and identified pleural effusion as a powerful predictor of RP-ILD in individuals with IIM-ILD. Meanwhile, we found a strong correlation between pleural effusion and unfavourable disease phenotypes in IIM, including increased systemic inflammatory response. Pleural effusion was also discovered to be an independent predictor of higher mortality risk in IIM.

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