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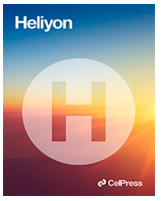

Research article

HRCT findings predict 1-year mortality in patients with acute exacerbation of idiopathic inflammatory myopathies-associated interstitial lung disease

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ABSTRACT

Background: Acute exacerbation of idiopathic inflammatory myopathies-associated interstitial lung disease (AE-IIM-ILD) is a significant event associated with increased morbidity and mortality. However, few studies investigated the potential prognostic factors contributing to mortality in patients who experience AE-IIM-ILD.

Objectives: The purpose of our study was to comprehensively investigate whether high-resolution computed tomography (HRCT) findings predict the 1-year mortality in patients who experience AE-IIM-ILD.

Methods: A cohort of 69 patients with AE-IIM-ILD was retrospectively created. The cohort was 79.7 % female, with a mean age of 50.7. Several HRCT features, including total interstitial lung disease extent (TIDE), distribution patterns, and radiologic ILD patterns, were assessed. A directed acyclic graph (DAG) was used to evaluate the statistical relationship between variables. The Cox regression method was performed to identify potential prognostic factors associated with mortality.

Results: The HRCT findings significantly associated with AE-IIM-ILD mortality include TIDE (HR per 10%-increase, 1.64; 95%CI, 1.29–2.1, $p < 0.001$; model 1: C-index, 0.785), diffuse distribution pattern (HR, 3.75, 95%CI, 1.5–9.38, $p = 0.005$; model 2: C-index, 0.737), and radiologic diffuse alveolar damage (DAD) pattern (HR, 6.37, 95 % CI, 0.81–50.21, $p = 0.079$; model 3: C-index, 0.735). TIDE greater than 58.33 %, diffuse distribution pattern, and radiologic DAD pattern correlate with poor prognosis. The 90-day, 180-day, and 1-year survival rates of patients who experience AE-IIM-ILD were 75.3 %, 66.3 %, and 63.3 %, respectively.

Conclusion: HRCT findings, including TIDE, distribution pattern, and radiological pattern, are predictive of 1-year mortality in patients who experience AE-IIM-ILD.

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1. Introduction

Interstitial lung disease (ILD) is the most common and severe complication among the multiple extra-muscular involvements in patients with idiopathic inflammatory myopathy (IIM), resulting in significantly increased morbidity and mortality [1,2]. Acute exacerbation (AE) is a life-threatening event in patients with ILD. Patients who experience AE usually require immediate hospitalization and often intensive critical care. However, only a few studies [3,4] have investigated the AE of IIM-ILD. Liang J et al. [3] reported an incidence of 13.3 % AE in IIM-ILD patients with a short-term mortality rate of 39.1 % in 665 subjects. Accurate risk stratification of morbidity and mortality in patients who experience an AE of IIM-ILD (AE-IIM-ILD) is critical to facilitate optimal clinical decisions and enable timely intervention to reduce mortality. Cao H and colleagues [4] assessed the gender-age-physiology-ILD (GAP-ILD) model in predicting survival in patients who experience AE-IIM-ILD. However, the direct application of this model to patients with IIM-ILD is controversial due to the racial disparities, follow-up time, and inappropriate weighting of lung physiology variables [5]. In particular, the ILD subtype in the GAP-ILD model includes several disease classifications, making the GAP-ILD inaccurate and even unsuitable for evaluating a specific disease.

High-resolution computed tomography (HRCT) is the most sensitive imaging modality to diagnose ILD and is crucial in guiding treatment decision-making by providing lung involvement details. The HRCT findings of IIM-ILD can be complex and varied but typically show abnormalities in the subpleural and basilar regions of the lungs, including ground-glass opacification (GGO), consolidation, reticulation, traction bronchiectasis, and honeycombing, with nonspecific interstitial pneumonia and organizing pneumonia being the most common radiologic patterns, while other patterns, such as usual interstitial pneumonia, can also occur. Different radiological findings are usually associated with varied disease severity and patient outcomes [1,6-8]. Previous studies demonstrated

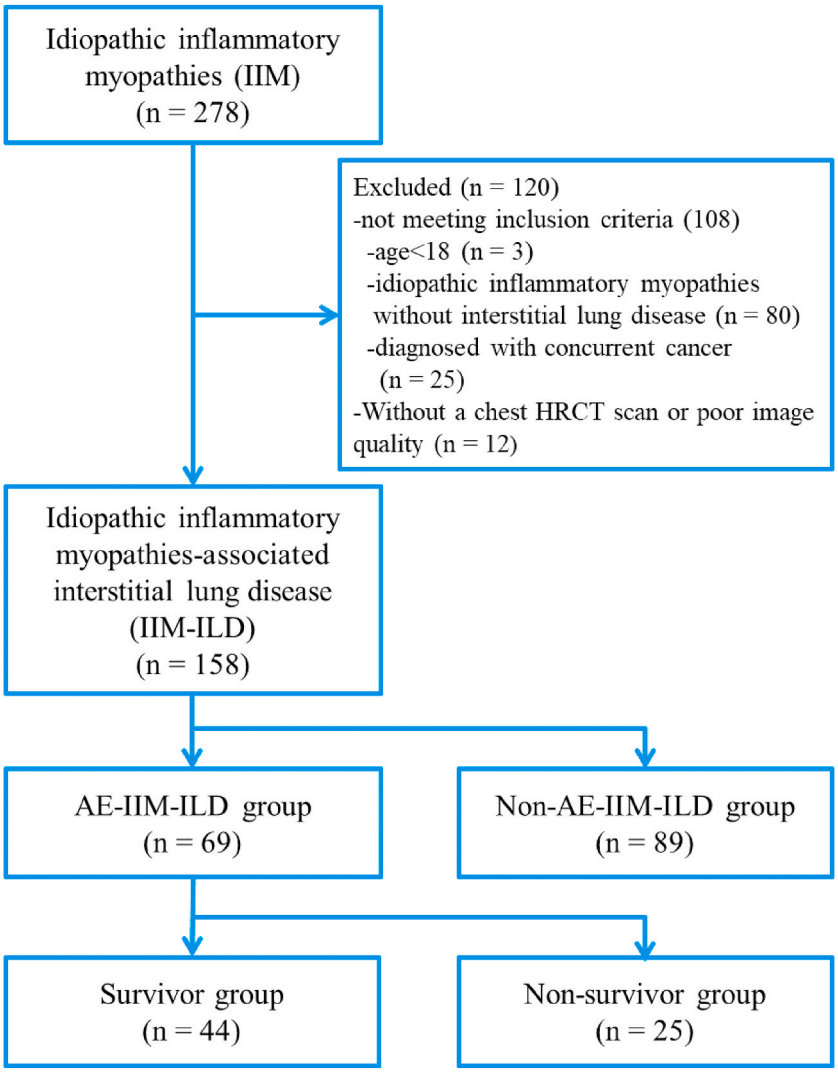

Fig. 1. Flow chart of eligible patients. AE = acute exacerbation, HRCT = high-resolution computed tomography.

the potential of HRCT imaging in predicting the outcome of IIM-ILD patients [6,8]; however, the conclusions of these studies are inconsistent. Tanizawa et al. [6] reported that the lower lung distribution pattern of consolidation/GGO on HRCT at diagnosis was an independent predictor of 90-day mortality in patients with dermatomyositis/polymyositis (DM/PM)-associated ILD, while the disease extent on HRCT had no predictive value. Another study by Zou et al. [8] showed that the global extent of the ILD-characteristic abnormalities in HRCT is associated with 1-year mortality of acute ILD in clinically amyopathic dermatomyositis patients. A possible explanation for the different conclusions may be a limited understanding of the statistical relationship among the HRCT findings. Additionally, whether and to what extent HRCT findings contribute to mortality in patients who experience AE-IIM-ILD remains unclear and, to our knowledge, has not been reported. Based on prior studies, we hypothesized that HRCT findings could be prognostic factors of the 1-year mortality in patients who experience AE-IIM-ILD. Therefore, we aimed to comprehensively investigate whether HRCT findings, including total interstitial lung disease extent, distribution patterns, and radiologic ILD pattern, could predict the 1-year mortality in patients who experience AE-IIM-ILD and if these features can be used to build a reliable prognostic model.

2. Methods

2.1. Patients

This retrospective study was conducted following the Declaration of Helsinki and was reviewed and approved by the local ethics committee of our hospital (approval number: KYLLSL201312202). Written informed consent was waived due to the study's retrospective observational nature and the use of anonymous clinical and imaging data. Electronic medical records were retrospectively reviewed for 278 consecutive patients diagnosed with IIM in our hospital between January 2014 and December 2020 to create the study cohort. IIM was diagnosed according to the Bohan and Peter diagnostic criteria or the 2017 EULAR/ACR classification criteria [9,10]. The diagnosis of IIM overlaps with other systemic autoimmune diseases (overlap IIM) was made according to the corresponding criteria for specific diseases, such as rheumatoid arthritis (RA) [11], systemic sclerosis (SSc) [12], systemic lupus erythematosus (SLE) [13], and Sjogren's syndrome (SS) [14]. IIM-ILD was diagnosed following the ATS/ERS criteria [15,16]. AE was defined according to the newly proposed criteria by Fabrizio Luppi et al. [17] for rheumatic disease as (a) previous or concurrent diagnosis of ILD; (b) acute worsening or development of dyspnea with typically $<$ 1-month duration; (c) HRCT findings indicating new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern of ILD, and (d) deterioration not fully explained by cardiac failure, fluid overload, or disease-modifying antirheumatic drugs used. The new criteria did not require the exclusion of infection. Both the diagnosis of IIM-ILD and AE were reassessed for this study by the investigators and determined based on their consensus. Patients who met the diagnostic criteria with available HRCT at AE onset were included. Exclusion criteria included: (1) age $<$18 years old; (2) without a chest HRCT scan; (3) diagnosed with concurrent cancer. Consequently, 69 AE-IIM-ILD patients were finally included (Fig. 1). The cohort included 55 (79.7 %) females, with a mean age of 50.7 $\pm$ 10.0 years at AE onset.

2.2. Data collection

Clinical and laboratory data for all patients were obtained by reviewing the medical records. Clinical data include age, gender, diagnosis of IIM subtype, disease duration, smoking history, and comorbidities; laboratory data include white blood cell (WBC; reference range: 3.5-10 $\times$ 10^9/L), serum levels of C-reactive protein (CRP; reference range: $\leq$0.3 mg/dL) and lactate dehydrogenase (LDH; reference range: $<$225 U/L) at AE onset. Myositis-specific autoantibody (MSA) and myositis-associated autoantibody (MAA) profiles were obtained in 48 subjects, which were detected by immunoblotting assay at the disease onset of each patient. All patients received supplemental oxygen therapy, corticosteroids, and various immunosuppressant therapy (treatment information is detailed in Table S1). Survival status was obtained by reviewing the medical records and/or confirmed via telephone interviews. Patients were followed from AE onset until death or the end of follow-up on December 31, 2021. Patients alive at the end of the follow-up period or lost to follow-up were censored on the date of last known communication. Four patients were lost to follow-up at the 2nd, 4th, 7th, and 10th months after AE onset and were censored.

2.3. HRCT assessment

The HRCT examinations at AE were obtained within seven days (median, 0 days; range, 0–7 days) after the onset of symptoms. HRCT was performed at maximal inspiration, with patients in the supine position extending from the lung apices to below the costophrenic angles using a 64-slice or 256-slice spiral CT scanner. Scanning protocol: tube voltage 120 kV, automatic tube current, reconstruction matrix of either 512 $\times$ 512 or 1024 $\times$ 1024. Images were reconstructed from raw data at 1 mm-thick sections with 1 mm intervals using a high spatial-frequency algorithm. All images were anonymized and reviewed at window settings appropriate for viewing the lung parenchyma (window width, 1300 Hounsfield units [HU]; window level, $-$450 HU) and mediastinum (window width 400 HU, level 40 HU). Two senior thoracic radiologists (with 11 years and 24 years of experience, respectively) independently reviewed each HRCT in random order and were blind to the clinical information. The presence and extent of ILD in HRCT were evaluated according to the Fleischner Society's glossary of terms for thoracic imaging and Walsh's scoring systems [18,19]. Briefly, the extent of interstitial abnormalities of the lung on HRCT images was scored at six levels: (a) the aortic arch; (b) 1 cm below the level of the carina; (c) the right pulmonary venous confluence; (d) the midpoint between level 3 and level 5; (e) 1 cm above the dome of the right hemidiaphragm; (f) 2 cm below the dome of the right hemidiaphragm. The extent of interstitial abnormalities was scored to the nearest 5 % at each anatomical level. Total interstitial disease extent (TIDE) was reported as the mean of the six levels.

The radiologic ILD pattern on HRCT was assessed and classified into five categories [15,16]: (1) non-specific interstitial pneumonia pattern (NSIP), (2) organizing pneumonia pattern (OP), (3) NSIP/OP overlap pattern, (4) diffuse alveolar damage pattern (DAD), and (5) usual interstitial pneumonia pattern (UIP). The axial distribution pattern of parenchymal abnormalities was classified as peripheral when the findings were in the outer one-third of the lung and diffused when the findings were generalized. Axial distribution was classified as random when no distribution pattern was apparent [20]. Other abnormal signs on HRCT images, such as esophagectasia and pneumomediastinum, were also recorded. In case of disagreement, a third expert thoracic radiologist (with 30 years of experience) was consulted to reach a final consensus regarding HRCT image interpretation.

2.4. Statistical analysis

All statistical analyses were performed using R software (version 4.0.5). Continuous variables were expressed as means (standard deviation, SD) or medians (interquartile range, IQR) as appropriate. Categorical variables were given as numbers and percentages. The student's *t*-test or Mann–Whitney *U* test was used for continuous variables. Pearson's chi-square or Fisher's exact test was used for categorical variables. The difference was statistically significant when the two-sided *p*-value was less than 0.05.

The Cox proportional hazard analysis was used to identify prognostic factors contributing to mortality. All variables identified as clinically significant or statistically significant ($p < 0.05$) were included in the multivariate analysis model. Additionally, the statistical relationship between variables was assessed using a directed acyclic graph (DAG) (Fig. S1) before multivariate analysis [21]. Adjusted

Table 1
Demographic, laboratory, and high-resolution computed tomography data at acute exacerbation of interstitial lung disease in 69 patients with idiopathic inflammatory myopathies.

Variables	Overall (N = 69)	Survivor (N = 44)	Non-survivor (N = 25)	*p value*[b]
Age, y, mean (SD)	50.7 (10)	50 (10.6)	51.8 (8.9)	0.48
Sex (female), n (%)	55 (79.7)	33 (75)	22 (88)	0.327
Disease duration, m, median [IQR]	8 [3,18]	7 [3,18]	10 [6, 19.4]	0.118
Smoking history, n (%)				1.00
Never smoker	60 (87)	38 (86.4)	22 (88)	
Ever smoker	9 (13)	6 (13.6)	3 (12)	
Comorbidities, n (%)	55 (79.7)	33 (75)	22 (88)	0.327
IIM subtype (%)				0.595
DM	50 (72.5)	32 (72.7)	18 (72)	
PM	11 (15.9)	8 (18.2)	3 (12)	
Overlap IIM	8 (11.6)	4 (9.1)	4 (16)	
MAA and MSA profiles[a], n (%)				0.159
Anti-Ro52	20 (29)	11 (25)	9 (36)	
Anti-ARS	18 (26.1)	15 (34.1)	3 (12)	
Anti-Jo-1	13 (0.2)	12 (0.27)	1 (0.04)	
Anti-PL7	4 (0.1)	3 (0.06)	1 (0.04)	
Anti-EJ	1 (0.01)	0 (0)	1 (0.04)	
Anti-MDA-5	10 (14.5)	6 (13.6)	4 (16)	
Missing	21 (30.4)	12 (27.3)	9 (36)	
WBC, 10^9/L, median [IQR]	7.8 [5.4, 11.1]	6.9 [5.0, 10.8]	8.4 [7.5, 11.3]	0.12
CRP, mg/dL, median [IQR]	**22 [10, 54.7]**	**10.7 [10, 45.6]**	**43.5 [11.4, 129]**	**0.017**
LDH, U/L, median [IQR]	**443 [331, 656]**	**426 [311, 524]**	**594 [372, 833]**	**0.013**
TIDE, %, mean (SD)	**56.8 (19.9)**	**48.5 (17.4)**	**71.5 (15.2)**	**< 0.001**
CT distribution patterns, n (%)				**0.002**
peripheral	34 (49.3)	27 (61.4)	7 (28)	
random	12 (17.4)	9 (20.5)	3 (12)	
diffuse	23 (33.3)	8 (18.2)	15 (60)	
Radiologic ILD patterns, n (%)				**0.015**
NSIP	10 (14.5)	9 (20.5)	1 (4)	
OP	21 (30.4)	17 (38.6)	4 (16)	
NSIP/OP	11 (15.9)	6 (13.6)	5 (20)	
DAD	23 (33.3)	9 (20.5)	14 (56)	
UIP	4 (5.8)	3 (6.8)	1 (4)	
Esohagectasia, n (%)	41 (59.4)	27 (61.4)	14 (56)	0.856
Pneumomediastinum, n (%)	6 (8.7)	4 (9.1)	2 (8)	1.00

Definition of abbreviations: y, years; m, months; IIM, idiopathic inflammatory myopathies; DM, dermatomyositis; PM, Polymyositis; MAA, myositis-associated autoantibody; MSA, myositis specific autoantibody; Anti-ARS, anti-aminoacyl-tRNA synthetase (ARS) antibody; Anti-Jo-1, anti-histidyl tRNA synthetase; Anti-PL7, anti-threonyl tRNA synthetase; Anti-EJ, anti-glycyl-tRNA synthetase; Anti-MDA-5, anti-melanoma differentiation-associated gene 5 antibody; WBC, white blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase; ILD, interstitial lung disease; TIDE, total interstitial lung disease extent; CT, computed tomography; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; NSIP/OP, nonspecific interstitial pneumonia overlapping with organizing pneumonia; DAD, diffuse alveolar damage; UIP, usual interstitial pneumonia.

[a] 48 patients with the MAA and MSA profiles were assessed.

[b] the differences between survivors and non-survivors are analyzed by using Mann–Whitney *U* test or Chi-square test, or Fisher's exact test; significant *p* values are in bold ($p < 0.05$).

models were established on the base of the variable screen. Model 1 included the TIDE adjusting for intermediate factors (i.e., CT distribution pattern, radiologic ILD pattern) to explore the association between TIDE and outcome. Model 2 included the CT distribution pattern adjusting for intermediate factors (i.e., TIDE, radiologic ILD pattern) to assess the association between CT distribution and outcome. Model 3 included radiologic ILD pattern with adjusting for intermediate factors (i.e., TIDE, CT distribution pattern) to determine the association between radiologic ILD pattern and outcome. Since MAA and MSA profiles were only obtained in 48 patients, we did not include them in the Cox regression analysis to avoid weakening the strength of the statistical analysis. Treatments after AE onset were also excluded from multivariate analysis due to the mediation effect. The prognostic performance of the models was assessed using the concordance index (C-index). Survival analysis was performed using Kaplan-Meier curves with the log-rank test.

3. Results

3.1. Clinical characteristics and HRCT findings

Among 278 consecutive IIM patients, 158 (56.8 %) were diagnosed with IIM-ILD. Sixty-nine patients (24.8 %) experienced AE of ILD after their first admission to our hospital. The median time from IIM diagnosis to first AE onset was eight months (range, 3–18 months). Table 1 summarizes the demographic, clinical characteristics, and HRCT findings of the study patients. The prevalence of IIM subtypes: (1) DM (50, 72.5 %), (2) PM (11, 15.9 %), and (3) overlap IIM (8, 11.6 %). Among eight overlap IIM: (1) 3 cases overlapped with Sjogren's syndrome (SS), (2) 3 cases overlapped with rheumatoid arthritis (RA), and (3) 2 cases overlapped with systemic sclerosis (SSc). The mean follow-up time was 23.0 months (SD = 23.5). The treatments after AE onset varied between patients based on their conditions and clinicians' decisions. Non-survivors received more intravenous immunoglobulin (56.0 % vs.25.0, $p = 0.01$), mechanical ventilation (44.0 % vs. 4.5 %, $p < 0.001$), and less cyclophosphamide (4.0 % vs. 40.9 %, $p < 0.001$) than survivors (Table S1). The proportion of mechanical ventilation should be higher in non-survivors, but some critically ill patients and their

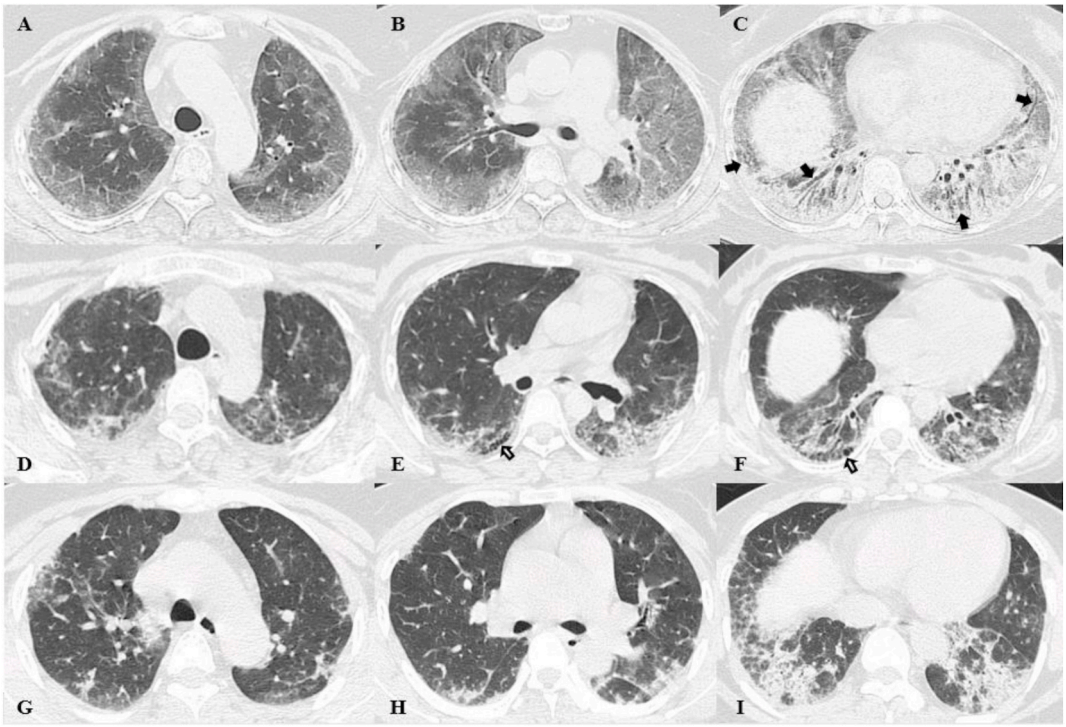

Fig. 2. **(A–C)**, High-resolution computed tomography (HRCT) images at the onset of acute exacerbation of idiopathic inflammatory myopathies-associated interstitial lung disease (AE-IIM-ILD) in a 58-year-old woman. The total interstitial disease extent (TIDE) was estimated to be 90.8 %. HRCT demonstrates new diffuse areas of ground-glass opacities (GGO) and consolidation at the lower dependent area, which agrees with a radiologic DAD pattern. Significant traction bronchiectasis and bronchiolectasis are also seen (black arrows). The patient died 12 days after the CT image. DAD, diffuse alveolar damage**. (D–F)**, HRCT images at the onset of AE-IIM-ILD in a 29-year-old woman. The TIDE was estimated to be 55 %. HRCT shows bilateral new GGO superimposed on underlying interlobular septal thickening, subpleural traction bronchiolectasis, and few honeycombing (which become more and larger 1year later, empty black arrows), which agrees with a radiologic UIP pattern. The patient remained alive for five years after AE onset. UIP, usual interstitial pneumonia. (**G-I**), HRCT images at the onset of AE-IIM-ILD in a 42-year-old woman. The TIDE was estimated to be 45 %. HRCT shows bilateral new GGO and consolidations superimposed on underlying subpleural interlobular septal thickening, which agrees with a radiologic NSIP/OP overlap pattern. The patient remained alive for one year after AE onset. NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.

families refused the invasive strategy. Twenty-five (36.2 %) patients died from respiratory failure or respiratory circulatory failure during follow-up (22 deaths caused by severe pneumonia due to infection (9) or rapid deterioration of IIM-ILD (13); 1 caused by acute pulmonary embolism; 2 caused by sudden cardiac arrest). The mean follow-up time in non-survivors and survivors was 2.3 months (SD = 2.62) and 34.8 months (SD = 21.9), respectively.

The serum CRP and LDH levels at AE onset were significantly higher in non-survivors compared to those in survivors [43.5 mg/dL (IQR 11.4–128.9) vs. 10.7 (10.0–45.6) ($p = 0.017$) and 594.0 U/L (IQR 372.0–833.0) vs. 425.6 (311.4–523.9) ($p = 0.013$), respectively] (Table 1). Age, sex, disease duration, smoking history, comorbidities, IIM subtype, MAA and MSA profiles, and the WBC count did not significantly differ between survivors and non-survivors.

The TIDE on HRCT was higher in non-survivors than in survivors [71.5 ± 15.2 % vs. 48.5 ± 17.4 % ($p < 0.001$), respectively] (Table 1) (Fig. 2(A-I)). There was a significant difference between the two groups in CT distribution patterns ($p = 0.002$). The typical patterns presented in non-survivors and survivors were diffuse (60.0 %) and peripheral (61.4 %), respectively. The radiologic ILD pattern significantly differed between survivors and non-survivors ($p = 0.015$). Most non-survivors presented the DAD pattern (56 %), whereas the survivors showed no specific radiologic ILD pattern. The prevalence of esophagectasia and pneumomediastinum did not significantly differ between the two groups.

3.2. Prognostic factors and models

Univariate Cox regression analysis revealed that the LDH and CRP serum levels, TIDE, CT distribution pattern, and radiologic ILD pattern at AE were significantly associated with mortality (Table 2).

Multivariable analysis of model 1 demonstrated that TIDE was an independent prognostic factor of mortality (hazard ratio [HR] per 10%-increase, 1.64; 95 % confidence interval [CI], 1.29–2.1, $p < 0.001$; Table 3) with a C-index of 0.785. An optimal cut-off value of TIDE was 58.33 % based on the Kaplan-Meier analysis. Patients with a high TIDE value (≥58.33 %) had a significantly worse outcome than those with a low TIDE value (<58.33 %) (log-rank test, $p < 0.001$) (Fig. 3A).

Model 2 showed the diffuse pattern was an independent prognostic factor (HR (compared with peripheral pattern), 3.75, 95%CI, 1.5–9.38, $p = 0.005$; Table 3) with a C-index of 0.737. There was a statistically significant difference in survival probability among different distribution patterns ($p < 0.001$) (Fig. 3B). Patients with the diffuse pattern on HRCT had a higher mortality risk than those with a random or peripheral pattern.

Model 3 revealed that the serum CRP level and the radiologic DAD pattern were independent prognostic factors with borderline statistical significance (HR per 1 mg/dL, 1.01, 95 % CI, 1.00–1.01, $p = 0.042$; HR (compared with NSIP), 6.37, 95 % CI, 0.81–50.21, $p = 0.079$; Table 3) with a C-index of 0.735. Different radiologic ILD patterns showed a significantly different survival probability ($p = 0.014$) (Fig. 3C). Patients with a DAD pattern on HRCT showed the most unfavorable outcome, and the NSIP/OP overlap pattern took

Table 2
Univariate analysis with Cox proportional hazards regression models.

Variables	Per unit for HR	HR (95%CI)	*p value*
Age	1-year	1.01 (0.98–1.05)	0.458
Sex	Male	0.55 (0.16–1.84)	0.33
Disease duration	1-month	1.01 (1.00–1.02)	0.164
Smoking history			0.466
Never smoker	Reference	Reference	
Ever smoker	positive	1.07 (0.32–3.59)	0.908
Comorbidities	positive	1.88 (0.56–6.3)	0.304
IIM subtype			0.47
DM	Reference	Reference	
PM	PM	0.73 (0.22–2.49)	0.621
Overlap IIM	Overlap IIM	1.75 (0.59–5.18)	0.312
WBC, 10^9/L	1 (10^9/L)	1.07 (0.99–1.15)	0.089
LDH, U/L	**10 U/L**	**1.01 (1.00–1.02)**	**0.033**
CRP, mg/dL	**1 mg/dL**	**1.01 (1.00–1.01)**	**0.012**
TIDE	**10 %**	**1.72 (1.37–2.15)**	**< 0.001**
CT distribution patterns			
peripheral	Reference	Reference	
random	positive	1.32 (0.34–5.09)	0.69
diffuse	**positive**	**4.58 (1.86–11.26)**	**0.001**
Radiologic ILD patterns			0.014
NSIP	Reference	Reference	
OP	positive	1.98 (0.22–17.7)	0.542
NSIP/OP	positive	4.91 (0.57–42.01)	0.146
DAD	**positive**	**8.55 (1.12–65.1)**	**0.038**
UIP	positive	2.84 (0.18–45.35)	0.461
Esohagectasia	positive	0.86 (0.39–1.9)	0.712
Pneumomediastinum	positive	0.96 (0.23–4.09)	0.959

For definitions of abbreviations, see Table 1.
Significant *p* values are in bold ($p < 0.05$).

Table 3
Multivariate analysis with Cox proportional hazards regression models.

Model 1[a]	Per unit for HR	HR (95%CI)	*p value*
LDH, U/L	10 U/L	1.01 (1.00–1.02)	0.026
CRP, mg/dL	1 mg/dL	1.01 (1.00–1.01)	0.432
TIDE	**10 %**	**1.64 (1.29–2.1)**	**< 0.001**
Model 2 [b]	**Per unit for HR**	**HR (95%CI)**	***p value***
LDH, U/L	10 U/L	1.01 (1.00–1.02)	0.151
CRP, mg/dL	1 mg/dL	1.01 (1.00–1.01)	0.106
CT distribution patterns			
peripheral	Reference	Reference	
random	positive	1.6 (0.4–6.39)	0.507
diffuse	**positive**	**3.75 (1.5–9.38)**	**0.005**
Model 3 [c]	**Per unit for HR**	**HR (95%CI)**	***p value***
LDH, U/L	10 U/L	1.01 (1.00–1.02)	0.295
CRP, mg/dL	**1 mg/dL**	**1.01 (1.00–1.01)**	**0.042**
Radiologic ILD patterns			
NSIP	Reference	Reference	
OP	positive	1.68 (0.18–15.24)	0.646
NSIP/OP	positive	3.05 (0.33–27.93)	0.325
DAD	**positive**	**6.37 (0.81–50.21)**	**0.079**
UIP	positive	2.77 (0.17–44.46)	0.472

For definitions of abbreviations, see Table 1.
Significant p values are in bold ($p < 0.05$).
[a] Model 1 explored the prognostic value of TIDE in patients who experienced AE-IIM-ILD; CT distribution patterns and radiologic ILD patterns were not included due to the potential mediation; C-index = 0.785.
[b] Model 2 examined the prognostic value of CT distribution patterns in patients who experienced AE-IIM-ILD; TIDE and radiologic ILD patterns were not included due to the potential mediation; C-index = 0.737.
[c] Model 3 explored the prognostic value of radiologic ILD patterns in patients who experienced AE-IIM-ILD; TIDE and CT distribution patterns were not included due to the potential mediation; C-index = 0.735.

second place. In contrast, patients with the NSIP pattern showed the most favorable outcome.

3.3. Survival analysis

The 90-day, 180-day, and 1-year unadjusted cumulative survival after AE onset were 75.3 % (95 % CI 0.66, 0.86), 66.3 % (95 % CI 0.56, 0.79) and 63.3 % (95 % CI 0.53, 0.76), respectively (Fig. 3D). Patients with high TIDE value (≥58.33 %) had a 1-year unadjusted cumulative survival from AE onset of 33.3 % (95 % CI 0.20, 0.55), which was significantly lower than patients with low TIDE value (87 %, 95 % CI 0.77, 0.98) ($p < 0.001$). The 1-year unadjusted cumulative survival in patients with a diffuse distribution pattern and a DAD pattern on HRCT after AE onset was 34.8 % (95 % CI 0.20, 0.61) and 39.1 % (95 % CI 0.24, 0.65), respectively.

4. Discussion

The management of IIM-ILD remains a challenge for clinicians due to the complexity of the disease and the lack of generally accepted guidelines. Acute exacerbation of IIM-ILD is a life-threatening event and is attracting more attention. Early recognition of high-risk patients is essential to determine the appropriate therapeutic strategy for patients who experience AE-IIM-ILD. To our knowledge, this is the first study to comprehensively evaluate the value of HRCT findings in predicting the outcome of patients who experience AE-IIM-ILD. This study demonstrated that TIDE, distribution pattern, and the radiologic ILD pattern on HRCT were independent prognostic factors of 1-year mortality of patients who experienced AE-IIM-ILD. TIDE greater than 60 %, diffuse distribution pattern, and radiologic DAD pattern correlate with poor prognosis.

Previous studies have shown conflicting results on which HRCT findings predict the prognosis of patients with IIM-ILD [6-8]. One possible reason could be the lack of sophisticated statistical analysis of the relationship among variables before multivariable analysis. This study used DAG to explore the statistical relationship between variables before multivariable analysis (Fig. S1) and found that three main HRCT findings, including TIDE, distribution pattern, and radiologic ILD pattern, are mutually mediating variables to each other. Hence, we built three models based on different variable selections to investigate the HRCT findings in predicting the outcome of patients who experience AE-IIM-ILD.

According to our results, TIDE showed a robust performance in predicting the 1-year mortality of patients who experience AE-IIM-ILD. Involvement of more than 58.33 % of the lung parenchyma suggests an unfavorable outcome. In these cases, the semiannual accumulated survival rate was 40 %, and the 1-year accumulated survival rate was 33.3 %. This result should enable clinicians to readily stratify patients into high and low-mortality risk groups and help drive clinical decisions. Moreover, TIDE can be easily estimated visually by clinicians using HRCT images. Our results agree with previous studies on the AE of idiopathic pulmonary fibrosis (IPF). Akira, M. et al. [20], in a study involving 58 patients with AE-IPF, showed that the average overall CT extent in non-survivors

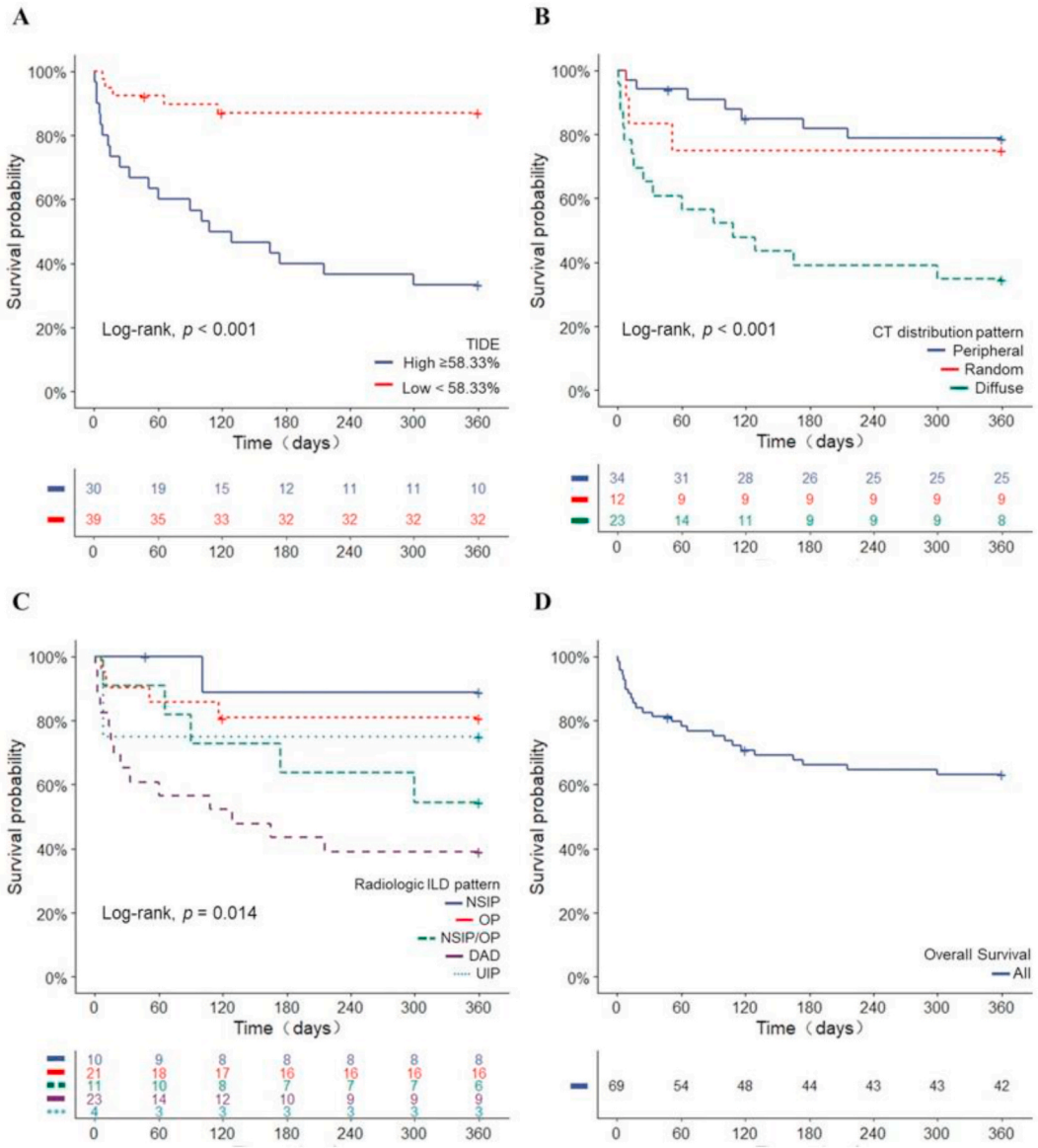

Fig. 3. A, B, C, Kaplan-Meier survival curves for patients who experience AE-IIM-ILD stratified by TIDE (A), CT distribution pattern (B), and radiologic ILD pattern (C); D, Overall survival of patients with AE-IIM-ILD. AE-IIM-ILD = acute exacerbation of idiopathic inflammatory myopathies-associated interstitial lung disease; TIDE = Total interstitial disease extent; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; NSIP/OP, nonspecific interstitial pneumonia overlapping with organizing pneumonia; DAD, diffuse alveolar damage; UIP, usual interstitial pneumonia.

was 58 ± 15 %. Possibly, when 58.33 % of the lung parenchyma is involved, it becomes a watershed for the patient's outcome. Fujimoto K. et al. [22] analyzed 60 patients with AE-IPF and reported that high HRCT image extent (HRCT score ≥245) correlates with poor prognosis. Indeed, it is essential to bear in mind the possible bias in this result with a small sample size, and future studies with more samples are needed to confirm our findings.

Concerning the CT distribution pattern, we found the diffuse pattern was a considerable prognostic and discriminative feature for separating non-survivors from survivors. In 23 patients with the diffuse pattern on HRCT images, 15(65.2 %) patients had died, with a 1-year cumulative survival rate of approximately 35 %. This suggests that the diffuse pattern is related to the most unfavorite outcome compared to the peripheral and random patterns. Peripheral and random patterns are usually related to limited lung involvement, which mainly correlates with radiologic/histopathological NISP or OP. Meanwhile, a diffuse pattern often indicates a poor situation of lung involvement and vulnerable lung function, corresponding to diffuse alveolar damage [23].

Radiologic ILD pattern has been recognized as a prognostic factor for the outcome of IPF and RA-ILD patients [24,25]. However, the predictive value of the radiologic ILD pattern was not confirmed in patients with IIM-ILD [3,26–28]. There may be two possible reasons

for this variability. First, these studies coarsely categorized the radiologic ILD pattern as UIP and non-UIP patterns. According to previous and our studies [1,7,29,30], such a classification is not appropriate for myositis because the UIP pattern is less frequently encountered in myositis. Second, most studies did not fully consider the potential mediating effects between variables. Our research found that the radiologic DAD pattern was the most potent independent prognostic factor for 1-year mortality. Kaplan-Meier analysis showed that patients with the DAD pattern carried the worst prognosis, followed by the NSIP/OP overlap pattern, while the NSIP pattern and OP pattern generally had a better prognosis. DAD pattern on HRCT is usually diffuse with patchy bilateral GGO and consolidation of the dependent lung in the exudation phase and progressing to traction bronchiectasis and architectural distortion in the organizing stage, which corresponds to the worst prognosis either in IPF or IIM-ILD [23,30–32]. The clinical outcome of the NSIP/OP overlap pattern remains controversial. Todd et al. [33] reported that the OP/NSIP overlap pattern was associated with unfavorable disease progression, which agrees with our study. However, another study showed that the OP components in NSIP did not affect prognosis [34].

The prevalence of AE in our cohort was 24.8 % (69/278), slightly higher than the published reports [3,35]. This discrepancy may be due to the following: First, our medical center is a large-scale comprehensive tertiary hospital. As a result, moderate and severe patients requiring critical or intensive care are often referred to our medical center. Second is the racial difference between various studies, given that IIM-ILD has a high prevalence in Asia. A recent meta-analysis reported that about 50 % of Asia patients with IIM develop ILD, whereas only 23%–26 % of Caucasian patients with IIM develop ILD [36]. Additionally, the new diagnostic criteria for AE-ILD in rheumatic disease no longer require the exclusion of triggered cases compared with the previous criteria [17]. In this study, the serum CRP and LDH levels were significantly higher in the non-survivors than in survivors. They were significantly associated with the prognosis of patients who experienced AE-IIM-ILD in univariate COX analysis. These findings are consistent with some previous studies [26,37–39]. Several studies have found that elevated CRP was an independent risk factor for developing ILD in patients with IIM [37, 38] and was associated with increased mortality risk [26]. A high LDH value was also associated with mortality of rapidly progressive ILD in IIM patients [38] and was an independent risk factor for prognosis [39].

There are several limitations to this study. First, this study's retrospective and observational nature could lead to inevitable selection bias. Second, the absence of MAA and MSA profiles in one-third of the enrolled patients significantly reduced the sample size when evaluating the two factors. Third, most patients at AE onset are critically ill and unable to perform pulmonary function tests on admission; thus, we are unable to draw a conclusion regarding its prognostic value. However, the main objective of this study was to clarify the prognostic value of HRCT findings in patients who experience AE-IIM-ILD. A large prospective series with adequate candidate variables is necessary to confirm our findings and bridge the gaps in scientific knowledge. Lastly, the HRCT assessment in our study involves a visually semi-quantitative and qualitative process, which can be somewhat subjective and time-consuming; nonetheless, our study lays a groundwork for future research utilizing objective quantitative CT, radiomics, or the promising artificial intelligence algorithm technology. We believe that these limitations should not affect the conclusion of this study, namely, the ability of the HRCT findings to predict mortality in patients who experience AE-IIM-ILD.

In conclusion, we demonstrated that TIDE, distribution pattern, and radiologic ILD pattern on HRCT are independent prognostic factors for the mortality of patients who experience AE-IIM-ILD. In particular, the chance of unfavorable outcomes is significantly high in subjects with interstitial abnormalities that involve more than 58.33 % of the lung parenchyma, presenting with a diffuse distribution pattern and radiologic DAD pattern.

Ethics approval statement

This study was conducted following the Helsinki Declaration and was reviewed and approved by the Human Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, with approval number: [KYLLSL201312202]; Written informed consent was not required due to the retrospective observational nature of this study and the use of anonymous clinical and imaging data.

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Data availability statement

The dataset supporting the findings of this study is available from the corresponding author upon reasonable and justified request.

CRediT authorship contribution statement

Jingping Zhang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Liyu He:** Validation, Methodology, Formal analysis, Data curation. **Tingting Han:** Validation, Investigation, Data curation. **Jiayin Tong:** Validation, Investigation, Data curation. **Jialiang Ren:** Validation, Methodology, Formal analysis. **Jiantao Pu:** Writing – review & editing, Validation, Methodology, Formal analysis. **Ming Zhang:** Validation, Supervision, Resources, Investigation. **Youmin Guo:** Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Chenwang Jin:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31510.

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