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ORIGINAL RESEARCH

Predicting Survival Across Acute Exacerbation of Interstitial Lung Disease in Patients with Idiopathic Inflammatory Myositis: The GAP-ILD Model

Heng Cao · Caijuan Huan · Qin Wang · Guanhua Xu · Jin Lin · Jianying Zhou

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ABSTRACT

Introduction: Risk prediction is challenging in patients with idiopathic inflammatory myopathies (IIM) and acute exacerbation of interstitial lung disease (AE-ILD) because of heterogeneity and patient-specific variables. Our objective was to assess whether mortality is accurately predicted in patients with IIM and AE-ILD by using the gender age physiology ILD (GAP-ILD) model, a clinical prediction model that was previously validated in patients with idiopathic pulmonary fibrosis.

Methods: A retrospective cohort study was conducted in the First Affiliated Hospital, Zhejiang University, wherein 60 consecutive patients with IIM and AE-ILD admitted between February 2011 and April 2019. The GAP-ILD was assessed retrospectively on the basis of gender, age and pulmonary function test.

Results: Patients with AE-ILD (n = 60) were identified and collected, 26 deaths occurred during follow-up, and the non-survivors group presented a higher level of GAP-ILD index (P = 0.005), bacterial infection (P = 0.013), and myositis disease activity assessment (MYOACT) (P = 0.031). The subsequent multivariate logistic regression analysis of overall mortality in AE-ILD revealed that bacterial infection (OR 5.275, P = 0.037) and GAP-ILD index (OR 2.292, P = 0.011) conferred significant risk of mortality. The GAP-ILD index was able to separate patients with AE-ILD into two groups with a statistically significant difference in survival rate (log rank P = 0.002). Satisfactory mortality estimation was maintained in the corresponding GAP-ILD index across the AE-ILD group.

Conclusion: The GAP-ILD model preforms well in risk prediction of mortality among patients with IIM and AE-ILD. Pulmonary bacterial infection can also be taken as an initial predictor of poor prognosis in patients with IIM and AE-ILD that must be taken seriously.

Keywords: Acute exacerbation of interstitial lung disease; Interstitial lung disease; Myositis; Prognosis; Survival

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H. Cao · Q. Wang · G. Xu · J. Lin (✉)
Department of Rheumatology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
e-mail: linjinzju@zju.edu.cn

C. Huan · J. Zhou (✉)
Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
e-mail: zjyhz@zju.edu.cn

Key Summary Points

Risk prediction is challenging in patients with idiopathic inflammatory myopathies (IIM) and acute exacerbation of interstitial lung disease (AE-ILD).

Our objective was to assess whether mortality is accurately predicted in patients with IIM and AE-ILD by using the gender age physiology ILD (GAP-ILD) model.

Our study showed that the GAP-ILD model preforms well in risk prediction of mortality among patients with IIM and AE-ILD.

Pulmonary bacterial infection is also an initial predictor of poor prognosis in patients with IIM and AE-ILD that must be taken seriously.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13042142.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of connective tissue diseases (CTD) which are frequently complicated by interstitial lung disease (ILD) [1]. Among the different myositis subtypes, polymyositis (PM), dermatomyositis (DM), and clinically amyopathic dermatomyositis (CADM) are most frequently associated with ILD. In published studies, ILD has been identified to be associated with worse outcomes and increased mortality [2–4]. Risk prediction in patients with IIM-ILD is challenging for clinicians because of heterogeneity in disease-specific and patient-specific variables. The clinical course and treatment response of IIM-ILD are quite heterogeneous, among which the complication of acute exacerbation ILD (AE-ILD) can be more devastating. It is thus critical to identify predictive factors of unfavorable outcome in patients with IIM and AE-ILD.

A number of studies have identified potential risk factors associated with unfavorable outcome in patients with IIM-ILD, and have reported associations between unfavorable outcome and older age, hypoxemia, anti-melanoma differentiation associated gene 5 body, a lack of myositis, pulmonary physiology, and AE [3, 5]. Nevertheless, risk factors predicting the commonly unfavorable outcome in AE-ILD remained unclear.

Recently, the ILD-gender age physiology (GAP) model was utilized to predicted survival across idiopathic pulmonary fibrosis (IPF) and other chronic ILDs. Its predicted value in IIM-ILD, however, remains disputable [6, 7]. The aim of this study was to assess whether mortality is accurately predicted in patients with IIM and AE-ILD by using the GAP-ILD model as well as to explore a simple and clinically reliable tool for clinicians.

METHODS

Study Subjects

This was a retrospective cohort study conducted in the Qingchun division and Chengzhan division of the First Affiliated Hospital, Zhejiang University (FAHZJU) in China, wherein 60 consecutive patients IIM (PM, DM, and CADM) and AE-ILD were hospitalized from February 2011 to April 2019. The diagnosis of IIM was based on 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups [8]. Individuals were classified as IIM-ILD if they met American Thoracic Society/European Respiratory Society criteria, which was a multidisciplinary decision made by rheumatologists, respirologists, and radiologists [9]. AE-ILD was defined as follows in this study: previous or concurrent diagnosis of ILD, acute

worsening or development of dyspnea typically of less than 1 month duration, high-resolution computed tomography (HRCT) with new bilateral ground-glass opacity and/or consolidation, which could not be fully explained by cardiac failure or fluid overload [10]. As previously suggested, the occurrence of this clinical and radiological manifestation in a background of possible or inconsistent with usual interstitial pneumonia pattern was also considered diagnosis of AE in patients with CTD [11, 12]. Compared with the previous diagnostic criteria for AE-ILD proposed in 2007, the new criteria did not demand exclusion of infection since infection has been found to participate in the pathogenesis and progression of IPF [13, 14]. Diagnosis of bacterial, fungal, or tuberculosis (TB) infection was a comprehensive decision based on clinical symptoms, infection-related laboratory abnormalities, HRCT manifestation, and the essential positive result of etiological detection. The etiological detection referred to the culture of bronchoalveolar lavage fluid (BALF) and sputum before intravenous use of antibiotics or antifungal medications. Sputum specimen counted only if more than 25 squamous epithelial cells per low-power field were observed. In the detection of bacterial infection, the thresholds for positivity of quantitative cultures were defined as 10^5 cfu/ml for sputum culture and 10^4 cfu/ml for BALF, respectively [15, 16]. For patients with suspicious fungal infection, direct visualization and culture of sputum or BALF, BALF PCR testing, serum galactomannan antigen, and (1–3)-β-D-glucan assays were conducted [17]. Pulmonary TB is diagnosed on the basis of chest CT findings and positive acid-fast bacilli sputum smear [18]. Diagnosis of Epstein–Barr virus (EBV) or cytomegalovirus (CMV) infection relied on the screening of serum antibody and DNA copies.

The patient enrollment process is outlined in Fig. 1. The study population comprised 33 patients with DM, 16 patients with PM, and 11 patients with CADM. Patients were excluded if they had an active neoplasm or other connective tissue diseases at the time of diagnosis or loss of follow-up (less than 6 months). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Institutional Review Board (IRB) of the First Affiliated Hospital of

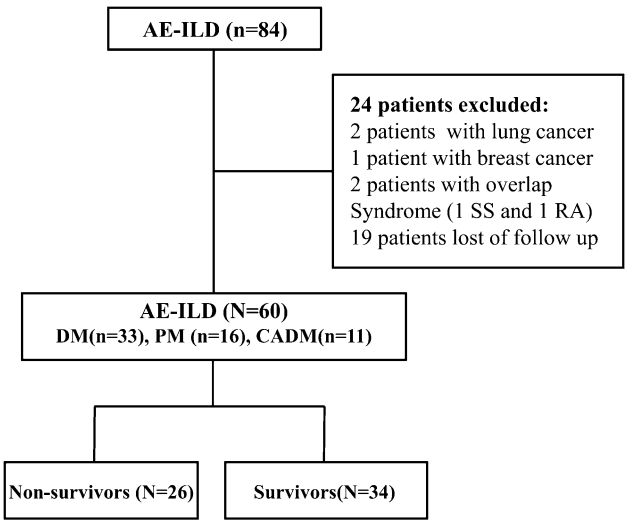

Fig. 1 Flowchart. The study population comprised 33 patients with DM, 16 patients with PM, and 11 patients with CADM. Twenty-six patients died during a follow-up of more than 6 months. AE-ILD acute exacerbation of interstitial lung disease, SS Sjögren's syndrome, RA rheumatoid arthritis, PM polymyositis, DM dermatomyositis, CADM clinically amyopathic dermatomyositis

Zhejiang University. The participants provided their written informed consent to participate in this study.

Clinical Evaluation

Clinical information was independently collected by two rheumatologists. Chest HRCT images were evaluated by two independent radiologists who were blinded to the patients' clinical information. The GAP-ILD model index was evaluated at the onset of AE. In order to assess whether mortality is accurately predicted by the GAP-ILD model and integrated patient-specific variables, data including demographic information, course of disease, clinical manifestations, laboratory findings, standardized pulmonary function tests (PFTs), and myositis disease activity assessment (MYOACT) [19] was acquired within the first week of hospitalization. The survival time was calculated from the first hospitalization due to AE onset.

The GAP-ILD Model

The GAP-ILD model was created by adding an ILD subtype variable to the original GAP model that accounted for better adjusted survival in patients with CTD-ILD, idiopathic nonspecific interstitial pneumonia, and chronic hypersensitivity pneumonia (Table 1). Points are assigned for each variable to obtain a total point score (range, 0–6) in IIM-ILD [20].

Table 1 The ILD-GAP model

	Predictor	Points
ILD	ILD subtype	
	IPF	0
	Unclassifiable ILD	0
	CTD-ILD/idiopathic NSIP	− 2
	Chronic HP	− 2
G	Gender	
	Female	0
	Male	1
A	Age, years	
	≤ 60	0
	61–65	1
	> 65	2
P	Physiology	
	FVC, % predicted	
	> 75	0
	50–75	1
	< 50	2
	DL_{CO}, %predicted	
	> 55	0
	36–55	1
	< 35	2
	Cannot perform	3
	Total possible points	8

ILD interstitial lung disease, *GAP* gender age physiology, *IPF* idiopathic pulmonary fibrosis, *CTD* connective tissue disease, *NSIP* nonspecific interstitial pneumonia, *HP* hypersensitivity pneumonia, *FVC* forced vital capacity, DL_{CO} diffusion capacity of the lung for carbon monoxide

Statistical Analyses

Statistical analyses were performed using SPSS 22.0 (Chicago, IL, USA) and R 3.6.1. Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed and median (quartiles) if skewed. Categorical variables were presented as numbers and percentage. Continuous variables were compared using independent sample *t* test or the Mann–Whitney *U* test. Unordered categorical variables were compared using the chi-square test or Fisher's exact test. Univariate and multivariate Cox proportional hazard logistic regression models were adopted to identify risk factors for unfavorable outcome in patients with AE-ILD. To be specific, only explanatory factors with a *P* value less than 0.05 in comparison or univariate analysis were entered into the multivariate Cox proportional hazard regression analysis. Results of the regression models are shown as the odds ratio (OR) and

95% confidence interval (CI). In addition, a receiver operating characteristic (ROC) curve analysis was performed to evaluate its predictive value for outcome or prolonged antibiotic therapy. On the basis of the cutoff value and preceding studies, we separated the GAP-ILD categories into two groups. Survival curves were drawn by using the Kaplan–Meier method and compared by using the log-rank tests. All tests were two-sided, and a *P* value less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 60 patients with IIM were identified with AE-ILD, and the patient characteristics are summarized in Table 2. During follow-up, the mortality rate in patients with IIM and AE-ILD was 43.3% ($n = 26$), with median survival time of 0.9 (range 0.2–20.0) months. Causes of death included refractory respiratory failure ($n = 19$, 73.1%), multiple organ failure ($n = 5$, 19.2%) ,and refractory circulatory shock ($n = 2$, 7.7%). Patients with unfavorable long-term outcome presented more frequently with bacterial infection ($P = 0.013$), higher GAP-ILD index ($P = 0.005$), and MYOACT ($P = 0.031$).

Prognostic Factors for Overall Mortality in AE-ILD

The multivariate logistic regression analysis of overall mortality in patients with IIM and AE-ILD revealed that bacterial infection and GAP-ILD index were significant risk factors of unfavorable long-term outcome. To be specific, univariate analysis showed that there were four factors associated with unfavorable outcome in patients with IIM and AE-ILD at the level of $P < 0.05$, namely GAP-ILD index ($P = 0.007$), MYOACT ($P = 0.037$), bacterial infection ($P = 0.020$), and tuberculosis infection ($P = 0.004$) (Table 3). The subsequent multivariate logistic regression analysis revealed that bacterial infection (OR 5.275, $P = 0.037$) and GAP-ILD index (OR 2.292, $P = 0.011$) were significantly correlated with unfavorable long-term outcome in patients with AE-ILD (Table 4).

Overall Survival Across GAP-ILD Index

ROC curve analysis revealed an area under curve of 0.728 and a cutoff value of 0.5 (Supplementary Fig. 1). Patients with IIM and AE-ILD were divided into two groups based on the GAP-ILD index 0–1 and 2–6. In the subsequent Kaplan–-Meier analysis, satisfactory mortality estimation was maintained in the corresponding GAP-ILD index across the AE-ILD group (log rank $p = 0.002$, Fig. 2).

DISCUSSION

The published studies reported unsatisfying survival rates of AE-ILD in CTDs and IPF range from 30% to 70% [21, 22]. White blood cell counts, age, lower baseline total lung capacity (TLC), forced vital capacity (FVC), carbon monoxide diffusing capacity (DL_{CO}), and extensive CT abnormalities at the time of AE were found to be associated with the survival of patients with CTD-ILD [23, 24]. In our study, nearly half of patients with AE-ILD died during follow-up. AE-ILD contributed significantly to the unfavorable outcome of patients with myositis. The poor survival of patients with IIM and AE-ILD is a great challenge. However, valuable predictive tools in these patients have remained insufficient. It is crucial to quantify disease severity and find a reliable prognostic assessment method in patients with IIM and AE-ILD. To date, this is the first study clarifying the predictive value of the GAP-ILD model in patients with IIM and AE-ILD. Novel composite physiologic indices and staging systems have been shown to reliably predict survival. The GAP model was previously demonstrated as an efficient risk prediction model in IPF [20]. In the last decade, the GAP model derived from IPF has been successfully applied to non-IPF fibrotic ILD [25]. Previous studies demonstrated that the GAP model was a mortality risk prediction tool in rheumatoid arthritis-associated ILD [26, 27]. Mango et al. also found that the GAP model

Table 2 Patient characteristics

	Non-survivors (*N* = 26)	**Survivors (*N* = 34)**	***P* value**
Age, years	60.5 ± 12.6	56.9 ± 10.2	0.234
Male, *n* (%)	10 (38.5%)	10 (29.4%)	0.461
Smoking	3 (11.5%)	3 (8.8%)	1
LDH, IU/L	441.0 (356.0, 675.0)	401.0 (316.3, 636.5)	0.596
CK, IU/L	154.0 (50.3, 475.5)	195.5 (82.3, 1239.5)	0.451
Ferritin	817.0 (600.6, 2683.8)	946.5 (150.0, 1957.4)	0.698
ESR, mm/h	23.0 (10.0, 41.8)	32.0 (9.5, 56.5)	0.455
Median survival time, months	0.9 (0.5, 1.5)	12.5 (5.75, 50.0)	*< 0.001*
MSA profile			
ANA	13 (50.0%)	25 (73.5%)	0.061
SSA	4 (15.4%)	8 (23.5%)	0.434
SSB	1 (3.8%)	2 (5.9%)	1
RNP	1 (3.8%)	0 (0.0%)	0.433
RIB	1 (3.8%)	1 (2.9%)	1
ACA	1 (3.8%)	0 (0.0%)	0.433
Anti-Ro52, n (%)	3 (11.5%)	9 (26.5%)	0.152
Anti-Jo-1, n (%)	1 (3.8%)	7 (20.6%)	0.122
Pulmonary function			
FEV1%	67.3 ± 18.5	65.6 ± 14.8	0.719
FVC, % predicted	63.5 ± 17.7	65.8 ± 15.0	0.628
TLC, L	3.0 (2.4,4.1)	3.1 (2.5,4.3)	0.752
FEV1/FVC	0.8 ± 0.1	0.8 ± 0.1	0.666
DL_{CO}, % predicted	47.6 ± 12.8	53.8 ± 14.4	0.131
Measures of disease severity			
GAP-index	2.0 (0.8, 2.3)	0.0 (0.0, 1.0)	*0.005*
MYOACT	11.3 ± 3.1	9.4 ± 3.5	*0.031*
Comorbidities			
Bacterial infection	9 (34.6%)	3 (8.8%)	*0.013*
Fungal infection	8 (30.8%)	16 (17.6%)	0.234
Tuberculosis infection	2 (7.7%)	0 (0.0%)	0.184
EBV/CMV infection	0 (0.0%)	2 (5.9%)	0.501
Gastrointestinal hemorrhage	4 (15.4%)	5 (15.7%)	1.000
Immunosuppressive therapy			

Table 2 continued

	Non-survivors (N = 26)	Survivors (N = 34)	P value
Steroid monotherapy	8 (30.8%)	13 (38.2%)	0.548
Steroid + DMARDs	7 (26.9%)	16 (47.1%)	0.112
Steroid + IVIG	8 (30.8%)	4 (11.8%)	0.068
Steroid + DMARDs + IVIG	3 (11.5%)	1 (2.9%)	0.186
IIM subtypes			
DM	15 (57.7%)	18 (52.9%)	0.714
CADM	5 (19.2%)	6 (17.6%)	1.000
PM	6 (23.1%)	10 (29.4%)	0.582

AE-ILD acute exacerbation of interstitial lung disease; *LDH* lactate dehydrogenase; *CK* creatine kinase; *ESR* erythrocyte sedimentation rate; *MSA* myositis specific antibody; *ANA* antinuclear antibody; *SSA* anti-Ro/SSA antibody; *SSB* anti-La/SSB antibody; *RNP* anti-RNP antibody; *RIB* anti-ribosomal P protein; *ACA* anti-centromere antibody; *FEV1* forced expiratory volume in 1 s; *FVC* forced vital capacity; *TLC* total lung capacity; DL_{CO} diffusing capacity of the lung for carbon monoxide; *GAP* gender age physiology; *MYOACT* myositis disease activity assessment visual analog scales; *EBV* Epstein-Barr virus; *CMV* cytomegalo virus; *DMARDs* Disease-modifying anti-rheumatic drugs; *IVIG* Intravenous immunoglobulin; DM dermatomyositis; *CADM* clinical amyopathic dermatomyositis; *PM* polymyositis

performed well in a systemic sclerosis associated ILD cohort and provides the best prognostic information [28].

To expand the scope of application of the GAP-ILD model, we validated it in a cohort of patients with IIM and AE-ILD. Tools for assessing disease activity like the MYOACT score, traditionally used to evaluate disease activity and predict long-term outcome, did not seem to efficiently predict the unfavorable outcome in AE-ILD. However, in our study, the GAP-ILD model was found to accurately predict the long-term outcome in patients with IIM and AE-ILD. The GAP-ILD model also included the GAP Staging System with proposed relevance [20]. Patients with IIM and ILD are often treated with high dose of immunosuppressive agents or biologics with unpredictable side effects [29]. The GAP-ILD model could help clinicians to make more wise decisions. For example, patients with a GAP-ILD index of 2–6 have a substantially higher mortality risk. After eliminating the complication of pulmonary infection, the clinicians should consider more aggressive treatment, such as high-dose glucocorticoid therapy, high-dose intravenous immunoglobulin therapy, or biologics. Meanwhile patients with a GAP-ILD index of 0–1 tend to have a lower mortality and they can thus take a lower-risk therapy and undergo routine clinical monitoring.

Preceding studies have proved that the GAP model performs well in all ILD subtypes [7, 26–28]. However, Brusca et al. found that the GAP-ILD was a poor predictor of mortality risk among individuals with IIM-ILD [6]. By narrowing down to IIM-ILD cases with AE-ILD, we successfully identified the predictive value of GAP-ILD. The patients with AE-ILD in our cohort are mostly hospitalized with a higher percentage in the CADM subgroup. This distinctive subgroup might be related to considerable complications of pulmonary infection and higher disease severity [30]. In addition, the patients in our study are all from the Chinese Han population, which differed from the two studies we discussed. This finding demanded to be verified in a larger population and different ethnic background.

On the other hand, pulmonary bacterial infection was also identified as a prominent predictor of poor prognosis in AE-ILD in our study. Historically, cases complicated with respiratory infection were excluded in AE of IPF or

Table 3 Univariate analysis for overall mortality in AE-ILD

	***P* value**	**HR value**	**95% CI**
Age, years	0.233	1.029	0.982 ~ 1.079
Male, *n* (%)	0.462	1.500	0.509 ~ 4.421
Smoking	0.729	1.348	0.249 ~ 7.295
LDH, IU/L	0.782	1	0.998 ~ 1.001
CK, IU/L	0.471	1	1.000 ~ 1.000
Ferritin	0.925	1	1.000 ~ 1.000
ESR, mm/h	0.223	0.987	0.966 ~ 1.008
MSA profile			
ANA	0.064	0.360	0.122 ~ 1.063
SSA	0.437	0.591	0.157 ~ 2.229
SSB	0.722	0.640	0.055 ~ 7.467
RNP	0.647	1.598	0.215 ~ 11.883
RIB	0.847	1.32	0.079 ~ 22.148
ACA	0.087	6.062	0.768 ~ 47.863
Anti-Ro52, n(%)	0.162	0.362	0.087 ~ 1.505
Anti-Jo-1, n(%)	0.091	0.154	0.018 ~ 1.344
Pulmonary function			
FEV1%	0.713	1.007	0.971 ~ 1.044
FVC, % predicted	0.621	0.991	0.955 ~ 1.028
TLC, L	0.658	0.891	0.534 ~ 1.486
FEV1/FVC	0.659	0.332	0.002 ~ 44.509
DLCO, % predicted	0.134	0.967	0.925 ~ 1.010
Measures of disease severity			
GAP-index	*0.007*	2.292	1.250 ~ 4.204
MYOACT	*0.037*	1.193	1.011 ~ 1.407
Comorbidities			
Bacterial infection	*0.020*	5.471	1.304 ~ 22.958
Fungal infection	0.238	2.074	0.617 ~ 6.695
Tuberculosis infection	*0.004*	9.996	2.097 ~ 47.640
EBV/CMV infection	0.467	0.046	0.000 ~ 181.190
Gastrointestinal hemorrhage	0.942	1.055	0.253 ~ 4.393
Immunosuppressive therapy			
Steroid monotherapy	0.549	0.718	0.243 ~ 2.120

Table 3 continued

	P value	HR value	95% CI
Steroid + DMARDs	0.116	0.414	0.138 ~ 1.242
Steroid + IVIG	0.077	3.333	0.877 ~ 12.666
Steroid + DMARDs + IVIG	0.219	4.304	0.421 ~ 44.017
IIM subtypes			
DM	0.868	1.069	0.490 ~ 2.330
CADM	0.702	1.21	0.456 ~ 3.211
PM	0.615	0.791	0.317 ~ 1.973

AE-ILD acute exacerbation of interstitial lung disease; *LDH* lactate dehydrogenase; *CK* creatine kinase; *ESR* erythrocyte sedimentation rate; *MSA* myositis specific antibody; *ANA* antinuclear antibody; *SSA* anti-Ro/SSA antibody; *SSB* anti-La/SSB antibody; *RNP* anti-RNP antibody; *RIB* anti-ribosomal P protein; *ACA* anti-centromere antibody; *FEV1* forced expiratory volume in 1 s; *FVC* forced vital capacity; *TLC* total lung capacity; DL_{CO} diffusing capacity of the lung for carbon monoxide; *GAP* gender age physiology; *MYOACT* myositis disease activity assessment visual analog scales; *EBV* Epstein-Barr virus; *CMV* cytomegalo virus; *DMARDs* Disease-modifying anti-rheumatic drugs; *IVIG* Intravenous immunoglobulin; *DM* dermatomyositis; *CADM* clinical amyopathic dermatomyositis; *PM* polymyositis

Table 4 Prognostic factors for overall mortality in AE-ILD

Factor	*P* value	HR value	95% CI
Bacterial infection	0.037	5.275	1.110 ~ 25.071
GAP	0.011	2.292	1.221 ~ 4.752

AE-ILD acute exacerbation of interstitial lung disease; *GAP* gender age physiology

ILD in previous papers, but the updated criteria of AE of IPF do not exclude respiratory infection [14]. The association between immunosuppressive treatment and severe infection, especially opportunistic infection, has been well documented in patients with CTDs [31, 32]. A potential infectious etiology was also reported to be responsible for one-third of patients with ILD and acute respiratory decline [22]. These might explain the correlation between infection and unfavorable outcome in AE-ILD. Previous studies demonstrated that severe infections

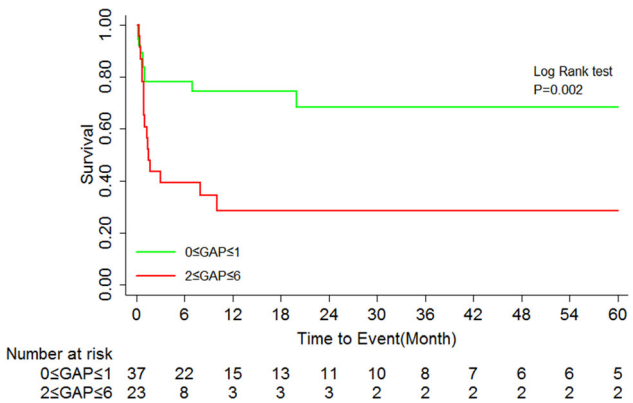

Fig. 2 Overall survival and long-term outcome in AE-ILD. Kaplan–Meier curves of survival in patients with IIM and AE-ILD based on the GAP-ILD index. AE-ILD acute exacerbation of interstitial lung disease, GAP gender age physiology

were associated with a worse prognosis in both IIM and IIM-ILD [33, 34]. This is the first study identifying the predictive role of infections in patients with IIM and AE-ILD.

The most significant limitations in our study are the small sample size and the retrospective and observational nature of the study. Furthermore, absence of records of myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs) in over half of the patients also prevented us from figuring out their roles in the development of unfavorable outcome in patients with AE-ILD. In the future, we intend to reevaluate the predictive value of the GAP-ILD model after taking MSAs and MAAs into consideration, or probe into its predictive value in the unfavorable anti-MDA5-antibody-positive subgroup. A larger and more representative prospective cohort study is as essential to confirm our findings and fill in the gaps.

CONCLUSION

Risk prediction is challenging in patients with IIM and AE-ILD owing to disease heterogeneity and patient-specific variables. The GAP-ILD model preforms well in risk prediction of mortality among patients with IIM and AE-ILD. Pulmonary bacterial infection can also be taken as an efficient predictor of poor prognosis in IIM-ILD that must be taken seriously.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Jianying Zhou and Jin Lin: conceptualization and methodology. Heng Cao: data curation, writing—original draft preparation. Caijuan Huan: writing—reviewing and editing. Qin Wang: visualization and investigation. Guanhua Xu: software and validation.

Disclosures. Heng Cao, Caijuan Huan, Qin Wang, Guanhua Xu, Jin Lin and Jianying Zhou have nothing to disclose.

Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Institutional Review Board (IRB) of the First Affiliated Hospital of Zhejiang University. The participants provided their written informed consent to participate in this study.

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

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