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Original Article

Clinical Significance of Age and Coexisting Lifestyle-related Diseases in ILD Patients with Acute Exacerbation

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ABSTRACT

OBJECTIVE: As the population ages, the impact of aging and comorbid lifestyle-related diseases on the prognosis of interstitial lung disease (ILD) has not been fully investigated. Therefore, we investigated the impact of age and comorbidities on the prognosis of patients with ILD who experienced acute exacerbations (AEs).

MATERIAL AND METHODS: We retrospectively reviewed the medical records and chest computed tomography scans of all consecutive ILD patients, with or without AE, between May 2015 and July 2025. The survival times of cases with and without AE were investigated.

RESULTS: Median survival time (MST) for 443 ILD cases was 10 years, while the MST for the 158 cases who developed AE was 2 months. The prognosis of cases who developed AE at age 80 years or older was significantly poorer than that of cases younger than 80 years. Among cases younger than 80 years, the survival curve for those who survived 3 months after the onset of AE plateaued. Favorable factors among cases who developed AE were age younger than 80 years and absence of comorbidities such as hypertension, diabetes mellitus, and malignancy.

CONCLUSION: For ILD patients who developed AE, "80 years of age" was the threshold age distinguishing good from poor prognosis. Some patients, particularly those with ILD who were diagnosed early, appeared likely to have an improved prognosis. Some AE patients, particularly younger patients, could be expected to have a good long-term prognosis if they survive a certain period of time.

KEYWORDS: Interstitial lung disease, acute exacerbation, age, comorbidities

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INTRODUCTION

Interstitial lung diseases (ILDs) are a variety of diverse entities that cause inflammation and fibrosis of the lung parenchyma.[1] ILDs, whether idiopathic pulmonary fibrosis (IPF) or connective tissue disease (CTD)-associated ILD,[2] can lead to acute exacerbations (AEs) characterized by the appearance of new pulmonary infiltrates in both lung fields and rapid progression of respiratory failure.[3] There is a generally accepted, very pessimistic view that the prognosis of ILD patients is poor.[4,5] Many studies have reported that the median survival time (MST) for patients who developed AEs was 1 to 4 months,[8-10] and for patients who did not develop AEs, it was only several years.[4-7] However, when assessing the prognosis of ILD, patient background factors such as age and comorbidities, as well as disease severity, should be considered. These results might be used to improve prognosis.

In developed countries, the population is aging, and as a result, changes are being observed in the onset of many diseases and the composition of patients.[11] These changes might also be occurring in ILD patients.[4,12-19] In general, the elderly have a high prevalence of lifestyle diseases,[11] which might reduce their ability to resist sudden onset and their tolerance to the

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side effects of ILD treatment. Although it is assumed that such a situation also exists in ILD patients, the impact of aging and coexisting lifestyle-related diseases on prognosis has not been thoroughly investigated.

Against this background, we conducted a study to investigate the influence of age and comorbidities on the prognosis of ILD patients with AE, aiming to characterize the current situation and clarify issues in ILD clinical practice.

MATERIAL AND METHODS

Patients

We retrospectively reviewed medical records and chest computed tomography (CT) scans from May 2015 to July 2025. First, we extracted data on patients diagnosed with ILD from the medical records at our two institutions during the study period. ILDs included usual interstitial pneumonia (UIP)/idiopathic interstitial pneumonia,[1,20-23] pleuroparenchymal fibroelastosis (PPFE),[21] combined pulmonary fibrosis and emphysema (CPFE)[22] and CTD-ILDs.[2] Patients with occupational ILDs, iatrogenic ILDs (e.g., drug-induced ILDs), sarcoidosis, pulmonary alveolar proteinosis, or lymphangioleiomyomatosis were excluded from this study. Additionally, patients with acute interstitial pneumonia were excluded due to their acute clinical course. Characteristics of CTD-ILD patients, such as age and gender, differed from those of idiopathic ILD patients; therefore, these characteristics were shown separately in the patient characteristics section. The chest CT images of the extracted patients were reinterpreted by chest physicians according to the diagnostic criteria of ATS.[1] For example, the presence of ground-glass opacities, traction bronchiectasis, and honeycombing was considered a UIP pattern, whereas the absence of these characteristics was considered a non-specific interstitial pneumonia (NSIP) pattern, PPFE pattern and CPFE pattern.[1,20-22] Chest CT images of CTD-ILD patients were also reinterpreted to determine whether they exhibited UIP or NSIP patterns.[1,20] Only patients whose images matched the imaging patterns of IPF, NSIP, CPFE, and PPFE were included in this study. In accordance with the ERS/ATS Statement 2025, an analysis of survival and prognosis was conducted for all ILD patients.[23] In addition, a sub-analysis of survival and prognosis in UIP patients, the most common type of idiopathic ILD, was performed based on morphologic patterns assessed by pathology and imaging.

Severity grading of ILD was determined according to the Japanese IPF disease severity classification; stage I: PaO_2 at rest ≥80 Torr, stage II: PaO_2 at rest = 70–80 Torr, and SpO_2 ≥93% during a 6-min walk test, stage III: PaO_2 at rest = 60–70 Torr (SpO_2 = 90–93% at rest), and stage IV: PaO_2 at rest <60 Torr (SpO_2 <90% at rest).[24,25]

Main Points

- For interstitial lung disease (ILD) patients who develop acute exacerbations (AEs), the age of 80 is the border between a better or poorer outcome.
- There are some patients, particularly those with ILD who are diagnosed early, who might achieve an improved outcome.
- Some patients with AE, particularly younger patients, can expect to have a good long-term prognosis if they can survive a certain period after AE onset.

The definition of AE was based on the diagnostic criteria for AE-IPF by Collard et al.[3] According to the definition used in this study, an AE was considered present if the following conditions were met: ILD was diagnosed at the time of the AE or had been previously diagnosed; acute progression of dyspnea occurred within the previous month; CT revealed new ground-glass opacities and/or infiltrates; and deterioration was not explained by heart failure or excess fluid accumulation alone. In analyses of survival time after the onset of AE, several cut-off values such as 30 days, 60 days, and 90 days have been used in some previous reports.[26,27] In the uni- and multivariate analyses of this study, survival or death at 30 days after the onset of AE was used as the cut-off period. In this study, if an ILD patient experienced two or more AEs, they were counted as two or more AE cases. For example, a patient who developed two AEs and was saved at least once was treated as two cases and analyzed.

This study investigated the impact of comorbidities that might affect the prognosis of ILD and its AEs, particularly major lifestyle-related diseases such as hypertension, diabetes, cardiovascular and cerebrovascular disorders, and malignant diseases.[28-34]

This study was reviewed and approved by the Institutional Ethics Committee of University of Tsukuba Hospital, Mito Medical Center (approval number: NO 25-47, date: June 2, 2025).

Statistical Analysis

In the statistical analysis of this study, the Mann-Whitney U test, a non-parametric test, was used to compare variables, including age, maximum primary tumor diameter, and clinical test values, between the two groups. The time at which ILD was confirmed by chest CT was used as the starting point, and survival status at the end of the study period was examined. For patients who were alive at the end of the study period, the observation period ran from the starting point. For patients who died during the study period or who were transferred to another hospital, the observation period extended from the starting point to the last follow-up. In this study, based on previous studies,[28-30] patients who survived for more than 30 days after the onset of AE were defined as "patients who could be saved," and patients who died within 30 days were defined as "patients who could not be saved." Comparisons between groups were made using the chi-square test and the Mann-Whitney U test. Survival analysis was performed using the log-rank test and the Cox proportional hazards model. A P value of <0.05 indicated a significant difference.

RESULTS

Characteristics of all the Interstitial Lung Disease Patients

Figure 1 shows the study flowchart for ILD patients. During the study period, 409 patients were diagnosed with ILD. Of these, 124 patients developed 158 AEs (26 patients had 34 AEs: 23 patients had 2 AEs, 1 patient had 3 AEs, 1 patient had 5 AEs, and 1 patient had 6 AEs). The median follow-up for all patients

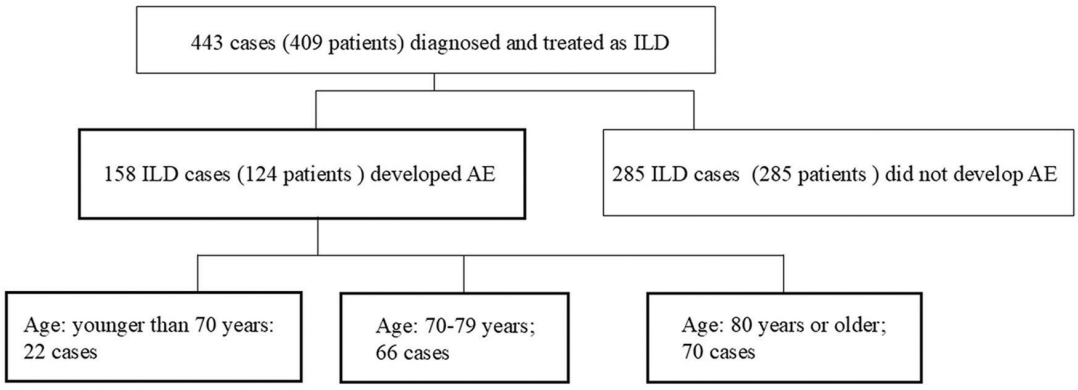

Figure 1. Study flow chart

ILD: Interstitial lung disease, AE: Acute exacerbation

was 48 months (range: 1–360 months). Among 443 cases in 409 ILD patients (including 26 patients with 34 AEs), 178 were male, and the median age at the time of ILD diagnosis was 73 years (range: 20–97 years). Smoking history was current in 37 cases, former in 241, never in 162, and unknown in 3. The comorbidities were as follows: 167 cases of hypertension, 128 of diabetes mellitus, 108 of cerebrovascular disease (including past and coexisting conditions), and 91 of malignant tumors (including past and coexisting conditions). ILD was classified as UIP in 286 cases, as NSIP and other conditions in 88 cases, and as collagen disease-related in 69 cases. The severity classification at the time of ILD diagnosis was I: 330 cases, II: 39 cases, III: 60 cases, and IV: 14 cases.

Characteristics of Interstitial Lung Disease Patients who Developed Acute Exacerbation

The median age at AE onset was 78 years (range: 54–97 years). By age group, 22 (13.9%) cases were under 60 years old, 66 (41.8%) were in their 70s, and 70 (44.3%) were 80 years or older. Patient characteristics by age are shown in Table 1. The older the patient group, the higher the proportion of men, patients with cardiovascular disease, and patients with a history of smoking. The median time from AE onset to consultation was 2 days (range: 1–15 days).

Do Not Attempt Resuscitation Acquisition and Treatment Details for Patients with Acute Exacerbation

Table 2 shows the rate of DNAR submission by patients with AEs and their families, as well as the treatment outcomes for AEs. There were no significant differences between age groups in the rates of "do not attempt resuscitation (DNAR)" submission or of treatment administered for AEs.

Table 1. Clinical characteristics of cases by age at onset of acute exacerbation

	Patient groups by age		***P* value**
	Younger than 80 years	**80 years or older**	
Number of cases	88	70	
Gender, male : female	74 ; 14	35 : 35	0.001
Comorbid diseases			
Hypertension	37	41	0.039
Diabetes	33	21	0.324
Cardio-cerebrovascular	17	17	0.450
Malignancy	18	13	0.767
Smoking habit, never : former : current	16 : 59 : 13	38 : 32 : 0	0.001
ILD			
Idiopathic ILD			
UIP	57	45	
NSIP or others	15	10	0.820
Collagen disease-related ILD	16	15	
ILD grade			
I : II : III : IV	57 : 11 : 17 : 3	36 : 6 : 20 : 8	0.080

ILD: Interstitial lung disease, UIP: Usual interstitial pneumonia, NSIP: Non-specific interstitial pneumonia

Survival in all 443 Interstitial Lung Disease Cases

During the follow-up period, 161 of the 443 cases died. The causes of death were respiratory failure in 143 cases and other causes in 18 cases (cancer in 10 cases, unknown in 6 cases, and cardiovascular in 2 cases).

The survival curves for the 443 cases are shown in Figure 2A. The MST for these cases was 120 months. Figure 2B shows survival time by severity of ILD at diagnosis. The MST for each group was 121 months for stage I, 120 months for stage II, 73 months for stage III, and 44 months for stage IV. There was a significant difference in survival time among these four groups ($P = 0.0001$).

Survival of Patients with and Without Acute Exacerbation

The MST for the 158 cases of AE was 2.0 months. Sixty-five cases died within 30 days of an AE, 25 died between 30 and 90 days, and 68 survived more than 90 days. The survival curves for patients by age at AE onset are shown in Figures 3A and 3B. The survival curves for patients under 70 years of age and for those in their 70s were nearly identical, whereas survival times for patients aged 80 years or older were worse than those for the other age groups. A statistically significant difference in survival times was observed between cases younger than 80 years and those 80 years or older ($P = 0.0012$).

Table 2. Comparison of treatments for AEs in cases stratified by age

A. Comparison of three case groups aged 70 and 80 years				
	Patient groups by age			***P* value**
	Younger than 60 years	**70-79 years**	**80 years or older**	
Number of cases	22	66	70	
Confirmation of intention not to receive life-sustaining treatment				
Present : absent	15 : 7	52 : 14	60 : 10	0.1786
Treatment administered				
Steroid pulse therapy	19	48	44	0.0926
NPPV	1	7	9	0.5469
Ventilator management	2	8	3	0.2482
B. Comparison of two case groups: younger than 80 vs. 80 years or older				
	Patient groups by age		***P* value**	
	Younger than 80 years	80 years or older		
Number of cases	88	70		
Confirmation of intention not to receive life-sustaining treatment				
Present : absent	67 : 21	60 : 10	0.1321	
Treatment administered				
Steroid pulse therapy	67	44	0.0697	
NPPV	8	9	0.4479	
Ventilator management	10	3	0.0744	

AE: Acute exacerbation, NPPV: Non-invasive positive pressure ventilation

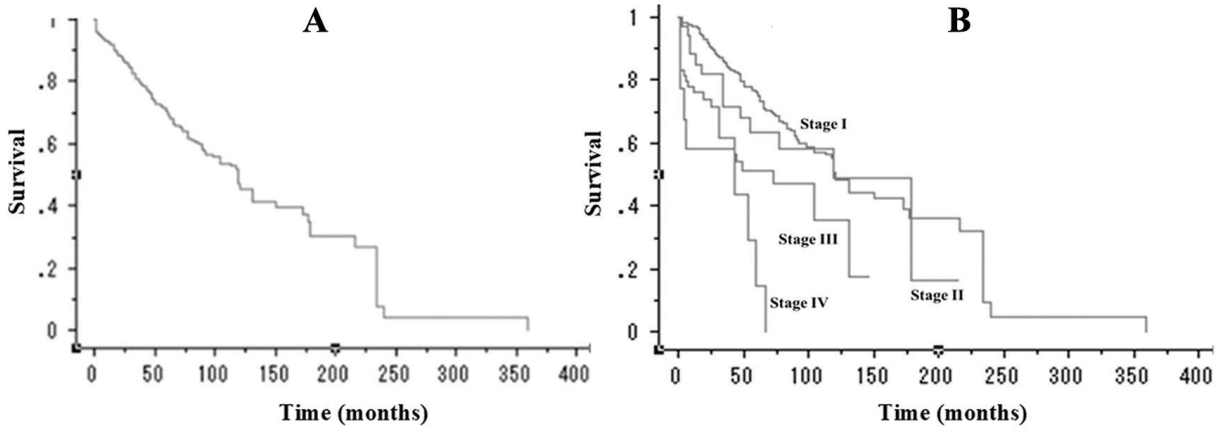

Figure 2. The survival curves for 443 interstitial lung disease (ILD) cases (A). The median survival time (MST) for these cases was 120 months. Survival curves according to the severity of ILD at the time of diagnosis (B). The MST for each group was 121 months for stage I, 120 months for stage II, 73 months for stage III, and 44 months for stage IV. There was a significant difference in survival time among these four groups ($P = 0.0001$)

Forty-seven cases died during the follow-up period without developing an AE. Causes of death in these cases were respiratory failure (36 cases), cancer (10 cases), and other (arrhythmia) (1 case).

Impact of Comorbidities on Prognosis

We investigated the impact of comorbidities on cases of AE (Table 3). Univariate analysis revealed that "younger than 80 years at the time of AE onset," "no concurrent hypertension," "no concurrent diabetes mellitus," "no concurrent malignant disease," and "imaging findings other than UIP" were significant factors; however, only the first four—excluding "imaging findings other than UIP"—were associated with a favorable prognosis.

Subgroup Analyses

Subgroup analyses were conducted in 102 patients with UIP (two-thirds of all cases), divided into two groups: those younger than 80 years and those 80 years or older. In univariate analysis, diabetes ($P = 0.0057$), malignant disease ($P = 0.0249$), and age 80 years or older ($P = 0.0271$) were found to be poor prognostic factors after the onset of AE. In multivariate analysis, only the presence of diabetes ($P = 0.0284$) was a significant poor prognostic factor, whereas the presence of malignant disease ($P = 0.0719$) and being 80 years or older ($P = 0.0555$) showed a trend toward a poor prognosis.

DISCUSSION

The present study included 443 ILD cases, including 158 with median ages of 73 years at ILD diagnosis and 78 years at AE onset, and yielded the following results: the MST for all ILD cases was 10 years, while the MST for AE-onset cases was 2 months. Elderly AE-onset cases were more likely to be male, to have comorbid hypertension, and to have a history of smoking. There were no age-related differences in requests for DNAR or in treatment administered for AE. However, the prognosis for cases in which AE developed at age 80 years or older was significantly poorer than for cases younger than 80 years. The survival curve for cases who survived 3 months after onset of AE plateaued. An age at onset of AE of 80 years or older and comorbidities such as hypertension, diabetes mellitus, and malignant disease were significant predictors of poor prognosis.

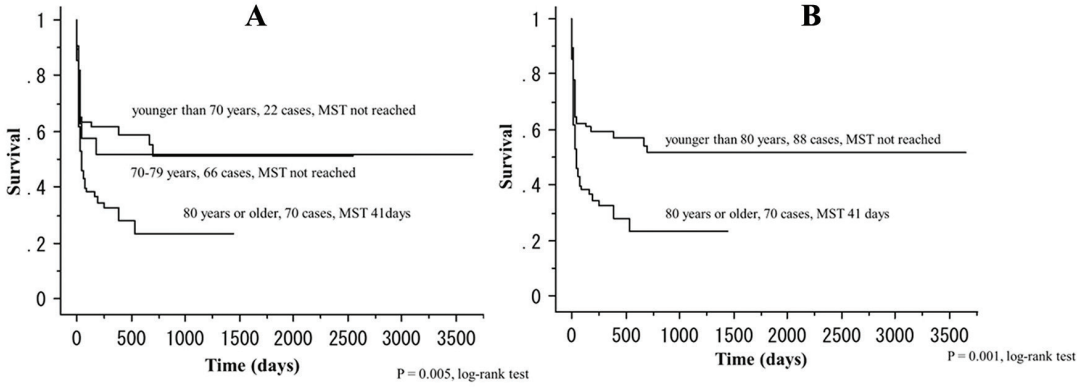

Figure 3. The survival curves by age at the time of acute exacerbation (AE) onset for cases younger than 80 years, in their 70s, and 80 years or older (A). The survival curves for patients under 70 years of age and in their 70s were nearly identical, while survival times for those 80 years or older were worse than those for these age groups. There was a statistically significant difference among the three age groups ($P = 0.0050$). The survival curves by age at the time of AE onset for cases younger than 80 years and 80 years or older (B). There was a statistically significant difference between survival times for cases younger than 80 years and those 80 years or older ($P = 0.0012$)

Table 3. Univariate and multivariate analysis of clinicopathological factors and survival after AE in ILD patients

	Univariate	Multivariate		
Variables	***P* value**	**HR**	**95% CI**	***P* value**
Female gender	0.3443			
Age, younger than 80 years	0.0012	1.788	1.145–2.791	0.0106
Never smoker	0.1323			
Comorbid, without hypertension	0.0298	1.715	1.089–2.700	0.0200
Comorbid, without diabetes	0.0043	0.473	0.283–0.791	0.0043
Comorbid, without cardio-cerebrovascular diseases	0.8218			
Comorbid, without malignancy	0.0164	1.817	1.116–2.959	0.0164
ILD type, other types than UIP	0.0288	1.563	0.987–2.474	0.0567
ILD grade I at the time of diagnosis	0.7742			
Therapy with anti-fibrotic drug	0.7804			

AE: Acute exacerbation, ILD: Interstitial lung disease, UIP: Usual interstitial pneumonia, HR: Hazard ratio, CI: Confidence interval

In developed countries, as the population ages, the median age at diagnosis for many diseases is changing. Even for ILDs, the median age at diagnosis is shifting to the 70s.[4,12-15] Although it is unclear whether this change is due to the aging of patients, the age at which AEs occur is also increasing, with recent reports showing a median age of AE onset of the mid-70s.[16-19] Takagi et al.[19] reported a study in which the median age at AE onset was 80 years old. In our study, the median age at ILD diagnosis and the age at onset of AE were 73 and 78 years, respectively. It was unclear how this aging affected the results. However, the results contained three notable findings, which we discuss below.

The first notable finding concerned the survival time of ILD patients. The results might have differed depending on the inclusion criteria used when conducting the survey, such as limiting ILD to IPF, limiting it to patients with UIP on imaging, or including CTD-ILD. However, regardless of the pathology or etiology of ILD, studies published within the last few years have also indicated that the MST from diagnosis for ILD patients was around 2 to 5 years.[4-6] Our current study, comprising 158 cases, showed that the MST from ILD diagnosis was 10 years. Furthermore, according to the Japanese IPF disease severity classification, the MST was 10 years for stages I and II, 6 years for stage III, and 3 years for stage IV. We compared our results with those of one of the most impactful studies, the Hokkaido study,[7] which included 553 IPF patients with a median age of 70 years at diagnosis. In this large-scale study, the cause of death in 40% of patients was respiratory failure due to AEs, and the overall MST was 35 months. The proportions of patients classified by the grading mentioned above were stage I, II, III, and IV, with 33.7%, 28.6%, 22.2%, and 15.7%, respectively.[7] The severity classification percentages of our cases were 58.9%, 10.8%, 23.4%, and 7.0% for stage I, II, III, and IV, respectively. The percentages of patients in stages I and II were 62.3% and 69.7%, respectively, indicating that our cases had a significantly higher proportion of patients in stages I and II. Notably, MST could vary greatly depending on patient grading. As mentioned above, previous studies, including the Hokkaido study, generally indicate that the prognosis for ILD is approximately 2–4 years from diagnosis.[6] However, it may be important to consider severity classification when evaluating MST, and our results suggest that, despite the advanced age of ILD patients, some patients, particularly those with less severe disease, may be expected to survive long-term. Therefore, early diagnosis and elimination of currently known risk factors, such as smoking, remain important. From this perspective, antifibrotic drug treatment[31] for patients with stage I or II ILD might also contribute to improving the prognosis. Additionally, it would be necessary to carry out activities to raise widespread awareness of these matters.

The second notable finding was the Kaplan-Meier survival curves for patients who developed AE. Cases aged 80 years or older had a poor prognosis, which was significantly different from that of cases younger than 80 years. We speculated that this result was not due to a significant difference in the proportion of comorbid conditions between those in the two age groups, but rather to a decline in the ability to cope with acutely progressive conditions, such as AEs. Notably, the prognosis curve for cases younger than 80 years who developed AE declined rapidly until approximately 3 months and then leveled off. This suggested that patients who survived up to 3 months after the onset of AE might include a subgroup expected to survive long-term.

The third notable result concerned factors affecting the prognosis of AE. In this study, the factors that affected the prognosis were older age; lifestyle diseases, such as diabetes mellitus and hypertension; and malignant diseases, such as lung cancer. Previous reports have highlighted the importance of lifestyle diseases such as these.[32-34] The metabolism and side effects associated with the administration of corticosteroids and immunosuppressants might affect prognosis. Further elucidation of the pathogenesis of AE and establishment of standard treatments are needed.

Study Limitations

We acknowledge that our study had some limitations. First, when interpreting the results, the retrospective nature of the study and the inclusion of heterogeneous ILD subtypes should be explicitly emphasized. The study period was long, allowing for an extended follow-up. While progress was made in the diagnosis and treatment of ILD during that time, it remained possible that these clinical advances were not fully taken into account. Second, the GAP scoring system is the most commonly used tool for predicting survival,[35] but it requires patient effort and assessment of diffusing capacity. In contrast, the severity classification used in this study used oxygen saturation measurement, a non-invasive assessment method, and this classification was originally developed for IPF.[24,25] The cohort in this study included a diverse group of ILD patients, including those with less severe disease. One limitation of this study is that this severity classification system has not been validated in ILD patient populations other than IPF. Third, we analyzed recurrent AEs as independent events. This might have introduced bias into the results. If an AE recovered to pre-onset levels and the interval between the onset and the next AE was at least several months, it was interpreted as a separate AE. However, it is unclear whether this interpretation was optimal, and future studies should consider optimal strategies for handling multiple AEs. Despite the limitations mentioned above, we believe we were able to provide results that more closely reflect actual clinical practice. The results of this study might indicate that many ILD patients aged 80 years or older have a decline in biological functions that cannot currently be quantified, such as the ability to tolerate and recover from acute illness.[36,37] However, this is beyond our current knowledge and will need to be addressed in future research.

CONCLUSION

As the population ages, both the age at ILD diagnosis and the age at onset of AE appear to be becoming older. The stage of ILD should be considered when assessing its prognosis. Among ILD cases who developed AE, 80 years of age was the threshold distinguishing good from poor prognosis. Among cases with AE onset before age 80, those who survive for a certain period may be expected to have a favorable long-term prognosis. In addition to aging, comorbid lifestyle diseases may influence the prognosis of ILD cases who develop AE, and managing these comorbidities during AE treatment may also be important.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Institutional Ethics Committee of University of Tsukuba Hospital, Mito Medical Center (approval number: NO 25-47, date: June 2, 2025).

Informed Consent: Comprehensive informed consent was obtained from each patient at the time of the diagnostic workup of ILD.

Footnotes

Authorship Contributions

Concept: H.S., R.H., Design: M.U., K.M., H.S., R.H., Data Collection or Processing: M.U., K.M., Y.M., N.K., S.O., H.S., Analysis or Interpretation: M.U., K.M., S.O., H.S., Literature Search: M.U., H.S., Writing: M.U., H.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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