EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

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Please cite this article as: Karayama M, Aoshima Y, Suzuki T, *et al*. A predictive model for acute exacerbation of idiopathic interstitial pneumonias. *Eur Respir J* 2023; in press (https://doi.org/10.1183/13993003.01634-2022).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

A predictive model for acute exacerbation of idiopathic interstitial pneumonias

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Take home message: A predictive model using existence of radiographic honeycombing, age >75 years, and serum lactate dehydrogenase level >222 U/L discriminated the risk of acute exacerbation in patients with idiopathic interstitial pneumonias.

Abstract

Background: Acute exacerbation of idiopathic interstitial pneumonias (AE-IIPs) induces permanent pulmonary dysfunction and is potentially lethal. The unpredictable occurrence of AE-IIPs remains an important clinical issue in the management of IIPs.

Methods: In this multicentre, retrospective, observational study, a predictive score for AE-IIPs was designed using clinical factors based on multivariate Fine–Gray analysis in patients with IIPs.

Results: Based on multivariate Fine–Gray analysis in an exploratory cohort of 487 patients with IIPs, the predictive score for AE-IIPs was determined as follows: 1 point each was added for honeycombing on high-resolution computed tomography (H), age >75 years (A), and lactate dehydrogenase level >222 U/L (L); the total score ranged from 0 to 3 (HAL score). The HAL score discriminated the risk of AE-IIPs with a c-index of 0.62 (95% confidence interval, 0.56–0.67); this discrimination was verified in a validation cohort of 402 patients with IIPs with a c-index of 0.67 (95% confidence interval, 0.60–0.73). In a combined cohort, the estimated cumulative risks for AE-IIPs at 1, 2, 3, 5, and 10 years were 1.9%, 3.5%, 5.1%, 7.7%, and 12.9% in the total score 0 group; 4.7%, 8.3%, 12.0%, 17.7%, and 28.4% in the total score 1 group; and 8.0%, 14.2%, 19.7%, 28.7%, and 43.0% in the total score ≥2 group. Subgroup analysis

revealed that the HAL score was applicable to patients with and without idiopathic pulmonary fibrosis.

Conclusions: The HAL score discriminated the risk of AE-IIPs and could aid in the management of IIPs.

Keywords: acute exacerbation, idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis, interstitial lung disease, honeycomb, pneumonitis

Background

Acute exacerbation of idiopathic interstitial pneumonias (AE-IIPs) has been defined as acute respiratory deterioration (with a duration typically less than 1 month) accompanied by new widespread alveolar abnormalities (bilateral ground-glass opacity and/or consolidation), in the absence of an alternative explanation such as cardiac failure or fluid overload [1, 2]. The reported incidence of AE-IIPs in patients with idiopathic pulmonary fibrosis (IPF) is approximately 10% per year [3–7]. Acute exacerbation also occurs in patients with non-IPF IIPs or secondary interstitial lung diseases (ILDs) [8–13]. Although the incidence and prognosis of AE-IIPs vary among IIPs, AE-IIPs is a potentially lethal event in any IIP. Even when patients avoid a fatal outcome, they often experience permanent pulmonary dysfunction because of pulmonary fibrosis caused by AE-IIPs.

The aetiology of AE-IIPs is unclear and its unpredictable occurrence remains an important clinical issue in the management of IIPs. Risk factors for AE-IIPs have been identified, including low forced vital capacity (FVC); low diffusing capacity of the lung for carbon monoxide (D_{LCO}); poor baseline oxygenation; radiological honeycombing; and/or increased levels of blood lactate dehydrogenase (LDH), Krebs von Lungen-6 (KL-6), or surfactant protein D (SP-D) [4, 6–9, 14–17]. However, the predictive abilities

of these factors have varied among studies and/or IIP entities. There are no established predictors for AE-IIPs. Because IIPs are a group of heterogeneous disease entities, the accurate prediction of AE-IIPs cannot be achieved using a single factor.

In contrast, scoring models with multiple clinical factors can provide clinical utility in predicting the overall survival of patients with IIPs. For example, the GAP index, composed of gender (i.e., sex), age, and physiology (% predicted FVC and D_{LCO}), has demonstrated good discriminative accuracy for the prognosis of IPF [18–20]. The model weights the survival risk of clinical factors using multivariate analyses to eliminate potential confounding factors; this facilitates the accurate prediction of survival among patients with IPF. However, because the model was designed for the prediction of overall survival in patients with IPF, it is inappropriate for predicting AE-IIPs.

The present study was conducted to establish a scoring model for predicting AE-IIPs in patients with IIPs. We identified risk factors for AE-IIPs using clinical data, determined the optimal combination of risk factors using multivariate analyses, and scored the selected factors according to their risk ratio. Furthermore, we verified the utility of the scoring model in another patient cohort.

Material and methods

Study design

This multicentre, retrospective, observational study followed the ethical standards of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Boards of Hamamatsu University School of Medicine (Hamamatsu, Japan, approval No. 20-173), Seirei Hamamatsu General Hospital (Hamamatsu, Japan, approval No. 3472), and Seirei Mikatahara General Hospital (Hamamatsu, Japan, approval No. 20-45).

Patients

The medical records of consecutive patients who were diagnosed with IIPs at the participating institutions between January 2001 and December 2020 were retrospectively analysed. The diagnosis of IIP was performed in accordance with American Thoracic Society/European Respiratory Society guidelines [21–23]. Only treatment-naïve patients were included because prior use of medications for IIPs might have influenced some predictive factors. Patients were excluded if they had ILDs secondary to known causes (e.g., collagen vascular diseases, sarcoidosis, or hypersensitivity pneumonia); if they received steroids, immunosuppressants, or antifibrotic agents for the treatment of IIPs at the first visit; and/or if they exhibited

acute exacerbation at the first visit. Patients in Seirei Hamamatsu General Hospital and Seirei Mikatahara General Hospital were regarded as the exploratory cohort; patients in Hamamatsu University Hospital were regarded as the validation cohort.

Data collection

The following clinical data were collected at the time of IIP diagnosis: age, sex, pack-year smoking history, history of dust exposure, laboratory data, pulmonary function, and the clinical and pathological diagnoses (pathological diagnosis was recorded only if performed). HRCT scans were obtained at three centres using various scanners at full inspiratory and spine position, with slice thickness from 1 to 3 mm and slice interval from 2.5 to 10 mm. All images were evaluated at standard window settings for visualization of the lung parenchyma (window level of −600 HU and window width of 1500 HU). Using HRCT images collected at the time of diagnosis, the presence of emphysema and honeycombing was evaluated by two experienced general radiologists (S.I. and N.Y.) who were blinded to all other patient data. The definitions of emphysema and honeycombing were established in accordance with the Fleischner Society guidelines [24]. Disagreements concerning the presence of emphysema and honeycombing were resolved by consensus decision in collaboration with a third

radiologist (S.G.). Autoimmune features were recorded according to the diagnostic criteria for interstitial pneumonia with autoimmune features [25]. The definition of AE-IIPs was based on an international working group report [1]. Additional details regarding the data correction are provided in Supplementary Method.

Statistical analysis

The time to the first AE-IIPs and overall survival were measured from the time of IIP diagnosis. Gray's test was used to analyse the time to the first AE-IIPs. Fine–Gray analysis was performed using clinical data to identify risk factors for AE-IIPs. Death prior to acute exacerbation was treated as a competing risk event.

Variables with *p*-values < 0.100 in univariate analyses were entered into multivariate analyses. When two variables exhibited strong correlations with each other (Pearson's correlation coefficient > 0.7), only one of the two was selected for multivariate analysis to avoid multicollinearity. Stepwise selection of variables for the predictive model was performed using the Akaike Information Criterion, Bayesian Information Criterion, and *p*-value-based methods. In Fine–Gray analysis, laboratory data (continuous variables) were converted into dichotomous categorical variables with cutoff values based on their upper normal limits.

To develop prediction scores for AE-IIPs, hazard ratios from the multivariate Fine–Gray analysis in the exploratory cohort were converted to logarithms, integral-multiplied, and rounded to the nearest integer [26]. The Harrell c-index was used in the Fine–Gray model to assess prediction model performance; 95% confidence intervals (95% CI) were obtained from bootstrap resampling of 2000 replicates. Time-dependent positive predictive values and negative predictive values were calculated using the Fine–Gray model. The predicted and observed cumulative incidence of AE-IIPs and overall survival at 1, 2, 3, 5, and 10 years were calculated using the Fine–Gray model. The predictive accuracy was verified in the validation cohort.

All values were analysed using R 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria). Additional details regarding the statistical analysis are provided in Supplementary Method.

Results

Patient characteristics

In the exploratory and validation cohorts, 549 and 453 patients with IIPs were screened for inclusion in the study. Sixty-two and 51 patients were excluded

because of unavailable data (no HRCT imaging data, n=25 and 18; no spirometric data, n=24 and 22; and no laboratory data, n=2 and 2) and the use of medications for IIPs at their first visit (n=11 and 9); thus, 487 and 402 patients, respectively, were included in the analysis (Figure 1). The clinical characteristics of the study cohorts are presented in Table 1. Both cohorts consisted mainly of men, more than half of the patients were aged >70 years, and approximately 30% of the patients had a history of smoking. Both cohorts generally had comparable demographic characteristics; however, the validation cohort had a significantly greater proportion of patients with a history of dust exposure (p<0.001) and significantly lower %FVC, percent predicted forced expiratory volume in 1 s, and $\%D_{LCO}$ values, compared with the values of the exploratory cohort (p<0.001, p<0.001, and p=0.031, respectively). In the exploratory and validation cohorts, 42.9% and 52.7% of the patients had %FVC <80%, respectively. Slightly more than 30% of patients had emphysema and slightly more than 40% of patients had honeycombing on chest HRCT images; these proportions were comparable between the two cohorts.

The proportions of types of IIPs were generally comparable between the two cohorts, except the validation cohort had a significantly greater proportion of patients with cryptogenic organising pneumonia (p=0.008). In the combined cohort, 317 (35.7%), 55 (6.2%), 55 (6.2%), 39 (4.4%), and six (0.7%) patients were diagnosed with IPF,

nonspecific interstitial pneumonia, pleuroparenchymal fibroelastosis, cryptogenic organising pneumonia, and desquamative interstitial pneumonia/respiratory bronchiolitis-associated interstitial lung disease, respectively. The remaining 416 patients (46.8%) had unclassifiable IIPs and slightly fewer than 10% of the patients had autoimmune features.

No patients had received steroids, immunosuppressants, or antifibrotic agents for the treatment of IIPs before the start of the study. During the observation period, 237 (26.4%), 349 (39.3%), and 118 (13.3%) patients in the combined cohort received antifibrotic agents, steroids, and immunosuppressants, respectively. Among the 237 patients who received antifibrotics, 99 (41.8%), 94 (39.7%), and 44 (18.6%) patients received pirfenidone, nintedanib, and sequential use of the two, respectively. The median observation time was 39.0 months (range, 1.0–238.9 months) in the combined cohort. The interobserver reproducibilities (κ statistics) for emphysema and honeycombing on HRCT were 0.74 (95% CI, 0.69–0.78) and 0.82 (95% CI, 0.78–0.86), respectively.

Predictive factors for AE-IIPs

During the study period, 103 and 56 patients developed AE-IIPs in the

exploratory and validation cohorts, respectively. Univariate Fine–Gray analysis identified the following predictive factors for acute exacerbation: older age; lower $\%D_{LCO}$; increased levels of LDH, KL-6, or SP-D; and presence of emphysema or honeycombing (Table 2). In multivariate Fine–Gray analysis, stepwise selection according to *p*-value identified the following independent predictive factors: presence of honeycombing, age >75 years, and LDH level >222 U/L (Table 2). Stepwise selection using the Bayesian Information Criterion identified high honeycombing and LDH as independent predictive factors; however, these factors were not employed for the final prediction model because the c-index of 0.59 was lower than the c-index of 0.62 obtained from the *p*-value selection. Stepwise selection using the Akaike Information Criterion did not identify a combination that consisted of significant factors. The results of the other candidate models in multivariate analyses are shown in Supplementary Table 1.

Predictive scores for AE-IIPs

Based on the risk ratio provided in Table 2, the predictive score for AE-IIPs was determined as follows: 1 point each was added for honeycombing (H), age >75 years (A), and LDH level >222 U/L (L); the total score ranged from 0 to 3 (HAL score)

(Figure 2a). A small proportion of patients had a total score of 3, and patients with total scores of 2 and 3 had comparable risks of AE-IIPs (Supplementary Figure 1). Therefore, the total scores of 2 and 3 were merged, and the patients were categorised into three groups: total score of 0, 1, and ≥2 (Figure 2b–d and Table 3). The HAL score discriminated the risk of AE-IIPs with a c-index of 0.62 (95% CI, 0.56–0.67); it demonstrated close agreement between the observed and predicted occurrence of AE-IIPs at each score level (Figure 2b, Table 3). In the validation cohort, the HAL score discriminated the risk of AE-IIPs with a c-index of 0.67 (95% CI, 0.60–0.73) (Figure 2c and Table 3). In the combined cohort, the estimated cumulative risks for AE-IIPs at 1, 2, 3, 5, and 10 years were 1.9%, 3.5%, 5.1%, 7.7%, and 12.9% in the total score 0 group; 4.7%, 8.3%, 12.0%, 17.7%, and 28.4% in the total score 1 group; and 8.0%, 14.2%, 19.7%, 28.7%, and 43.0% in the total score ≥2 group (Figure 2d and Table 3). In the combined cohort, the respective time-dependent positive predictive values of the HAL score at 1, 2, 3, 5, and 10 years were 6.4%, 10.8%, 15.6%, 22.9%, and 33.4% in the total score ≥1 group (vs. <1), whereas they were 7.6%, 13.7%, 20.8%, 30.2%, and 45.1% in the total score ≥2 group (vs. <2). The respective time-dependent negative predictive values at 1, 2, 3, 5, and 10 years were 98.9%, 96.6%, 94.8%, 93.1%, and 82.7% in the total score ≥1 group (vs. <1), whereas they were 96.0%, 93.2%, 90.6%,

86.3%, and 76.3% in the total score ≥2 group (vs. <2) (Table 4).

Subgroup analysis

Next, patients in the combined cohort were divided into two subgroups of IIPs: IPF and non-IPF. In the IPF group, the HAL score discriminated the risk of AE-IIPs (c-index=0.59, 95% CI, 0.54–0.64) (Figure 3a). The estimated cumulative risks at 1, 2, 3, 5, and 10 years were not estimable, 3.6%, 7.3%, 10.5%, and 16.2% in the total score 0 group; 5.0%, 11.6%, 19.3%, 27.4%, and 39.0% in the total score 1 group; and 6.3%, 14.4%, 23.2%, 32.5%, and 46.5% in the total score ≥2 group (Supplementary Table 2). Furthermore, in the non-IPF group, the HAL score discriminated the risk of AE-IIPs (c-index=0.63, 95% CI, 0.57–0.69) (Figure 3b). The estimated cumulative risks at 1, 2, 3, 5, and 10 years were 2.3%, 3.5%, 4.3%, 6.6%, and 11.5% in the total score 0 group; 4.8%, 7.0%, 8.6%, 13.1%, and 23.5% in the total score 1 group; and 8.6%, 13.2%, 15.7%, 23.3%, and 36.2% in the total score ≥2 group (Supplementary Table 2).

In the combined cohort, patients who did and did not receive antifibrotic therapy before the occurrence of AE-IIPs (antifibrotic and non-antifibrotic groups, respectively) were separately analysed. Sixteen patients who received antifibrotics after the occurrence of AE-IIPs were included in the non-antifibrotic group. In the antifibrotic

group (n=221) and non-antifibrotic group (n=668), 37 (16.7%) and 122 (18.3%) patients experienced AE-IIPs (p=0.686), respectively. In the both groups, the HAL score discriminated the risk of AE-IIPs (Figure 3c-d). In a separate evaluation of patients in the IPF groups who did and did not receive antifibrotics, there was a tendency toward an increased risk of AE-IIPs as the HAL score increased, regardless of antifibrotic treatment; however, the HAL score did not discriminate the risk of AE-IIPs, particularly when comparing between the scores of 1 and ≥2 (Supplementary Figure 2). Among patients in the non-IPF group who did not receive antifibrotics, the HAL score discriminated the risk of AE-IIPs; however, only 10 AE-IIPs occurred among patients in the non-IPF group who received antifibrotic treatment, which was insufficient to confirm the utility of the HAL score. Nevertheless, those patients also exhibited a tendency for an increased risk of AE-IIPs as the HAL score increased (Supplementary Figure 2). When patients were stratified according to %FVC of 70% or 80%, the HAL score discriminated the risk of AE-IIPs in all groups (Supplementary Figure 3).

A total of 113 (12.7%) patients in the combined cohort (34 and 79 in the exploratory and validation cohort, respectively) had CT images with a slice thickness from >1.5 to 3 mm. When we evaluated the HAL score in the remaining 776 patients who had CT images with a slice thickness from 1.0 to ≤1.5 mm, the HAL score

discriminated the risk of AE-IIPs (Supplementary Figure 4).

Model prediction of overall survival

When the HAL score was applied to overall survival, the model discriminated the risk of death with a c-index of 0.61 (95% CI, 0.58–0.64) (Figure 4 and Supplementary Table 3). The estimated survival rates at 1, 2, 3, 5, and 10 years were 97.0%, 92.3%, 88.0%, 84.1%, and 54.0% in the total score 0 group; 94.4%, 86.4%, 79.1%, 65.2%, and 32.3% in the total score 1 group; and 90.8%, 78.4%, 67.9%, 49.2%, and 15.4% in the total score ≥2 group (Supplementary Table 3).

Discussion

In the present study, univariate analyses revealed the following predictive factors for AE-IIPs: age; lower $\%D_{LCO}$; increased levels of serum KL-6, SP-D, and LDH; and presence of emphysema and honeycombing on HRCT images. Among them, multivariate analyses selected the scoring model using honeycombing, age >75 years, and LDH level >222 U/L, which discriminated the risk of AE-IIPs. The utility of the HAL score was also verified in the validation cohort. Subgroup analysis revealed that the HAL score could be applied to patients with and without IPF. Furthermore, the HAL

score discriminated the overall survival of patients with IIPs. The clinical factors employed in the HAL score were readily available in clinical practice; this simple model could be used for the stratification of AE-IIPs risk in the management of patients with IIPs.

Both honeycombing and LDH have strong predictive value among well-known risk factors, such as lower $\%D_{LCO}$ and increased levels of KL-6 and SP-D. Honeycombing and LDH were also selected as predictive factors in other candidate models selected by different stepwise methods (Supplementary Table 1). The presence of honeycombing is a hallmark of fibrotic changes in pulmonary tissue and an important finding for the radiological diagnosis of IPF [22]. There are two possible explanations for the predictive ability of the presence of honeycombing. First, the presence of honeycombing suggested a diagnosis of IPF, which has the highest risk of acute exacerbation among IIPs [3–7, 10, 22, 27, 28]. Second, radiological honeycombing itself is reportedly a risk factor for AE-IIPs in patients with and without IPF [8, 10, 16, 29–32]. Honeycombing is the result of progressive pulmonary fibrosis and is associated with disease severity in patients with IIPs. It is reasonable that the presence of honeycombing was a predictor of AE-IIPs across various IIP phenotypes.

An increased level of LDH, another strongly predictive factor selected in the

present study, is used to monitor disease activity in clinical practice and has been identified as a risk factor for AE-IIPs [14, 29, 33, 34]. LDH, an enzyme found in every organ, can indicate the occurrence of lung damage; therefore, it is used for the assessment of various IIPs. The disease-nonspecific utility of LDH presumably contributed to its predictive ability for AE-IIPs in various types of IIPs. Another possible explanation is that LDH had less confounding influence from other predictive factors, which allowed it to serve as a more effective independent predictor.

However, other factors significant in univariate analysis (e.g., lower $\%D_{LCO}$ and/or increased levels of KL-6 and SP-D) were not included in the optimal model according to multivariate analysis. Although they are controversial, these factors have been identified as predictors of AE-IIPs [4, 6–10, 14–17]. Lower $\%D_{LCO}$ and/or increased levels of KL-6 and SP-D are associated with IIP disease severity and/or activity. Therefore, these three factors might have confounding effects on honeycombing and LDH, which are strongly associated with AE-IIPs; these effects resulted in the exclusion of the three factors from the final predictive model. Notably, $\%D_{LCO}$, KL-6, and SP-D had weak but significant correlations with each other, as well as honeycombing and LDH.

The HAL score could discriminate the risk of AE-IIPs regardless of antifibrotic

treatment during the study period. Antifibrotic agents have been shown to reduce the risk of AE-IIPs, which might affect the natural occurrence of AE-IIPs [35]. However, the utility of the HAL score was maintained even in patients who received antifibrotics. This finding suggests that, for antifibrotic-naïve patients, the HAL score could provide supplemental information regarding the potential use of antifibrotic agents based on current clinical guidelines. Furthermore, after patients receive antifibrotics, the HAL score could continue to be used for stratification of AE-IIP risk.

The advantage of the HAL score is that it requires only simple clinical factors without precise classification of IIPs. The risks for AE-IIPs differ among IIP phenotypes; however, the phenotypic classification of IIPs is not simple in clinical practice. First, it is difficult to accurately diagnose the IIP phenotype in the initial examination. For example, some patients with IPF lack typical honeycombing on HRCT images at the early stage, although they eventually develop honeycombing with disease progression. Additionally, patients with advanced non-IPF IIPs sometimes develop radiological and pathological honeycombing that mimics IPF [22]. Second, surgical lung biopsy for the diagnosis of IIPs cannot be performed in some patients because of its invasive procedure[36]. Third, pathological findings can vary among lung sites in patients with IIPs. If surgical lung biopsy is not performed for representative lesions, it

is difficult to ensure an accurate diagnosis [37]. Furthermore, discordant diagnosis is frequent even among specialists [38]. The current model could provide cross-phenotypic utility for the prediction of AE-IIPs in patients with various IIPs.

Nevertheless, the c-index and positive predictive value of the HAL score were not sufficiently high for use as a prediction model. These findings may be related to the existence of other potential risk factors for AE-IIPs that were not included in the HAL score. Low FVC, low D_{LCO}, and high serum levels of KL-6 and SP-D have been identified as risk factors for acute exacerbation, although those factors were not included in the model based on multivariate analysis. Additionally, there may be unknown risk factors, such as genetic factors, detailed chest CT findings, the extent and localisation of CT abnormalities, bronchoalveolar lavage findings, or levels of serum biomarkers other than KL-6 and SP-D. Alternative predictive models might have been selected if we had included more detailed data concerning IIPs. Additionally, the positive predictive value of the HAL score was not sufficiently high to predict the incidence of AE-IIPs, possibly because of the low prevalence of AE-IIPs in the study cohort. Notably, the positive predictive value increased over time as the incidence of AE-IIPs increased. Nevertheless, the high negative predictive value indicates that the HAL score may be useful in the identification of patients with a low risk of AE-IIPs.

The HAL score does not completely predict the incidence of acute exacerbation with high accuracy, but it can be used to determine the approximate risk of AE-IIPs (based on three simple factors) in clinical practice.

The present study had three main limitations. First, the detection of honeycombing varied among HRCT scanners and observers. HRCT images were obtained at specific intervals (the interval ranged from 2.5 to 10 mm among the centres and scanners). Furthermore, approximately 13% of the study patients had a slice thickness from >1.5 to 3 mm. Mild honeycombing might have been missed in the thick and interspaced HRCT images. Although there was considerable interobserver reproducibility in terms of honeycombing detection, we could not guarantee complete consistency among observers. In fact, a certain level of disagreement regarding the detection of honeycombing among observers has been reported [39]. There is a need to understand the limit of honeycombing detection when interpreting the HAL score in clinical practice. Second, the present study only evaluated Japanese patients with IIPs. There are ethnic differences in the prevalence of ILDs and the risk of AE-IIPs [1, 5, 16, 40, 41]. Therefore, the optimal models for AE-IIPs may differ according to ethnicity. Third, differences in predictive utility among IIP phenotypes are unknown. Approximately half of the study patients had unclassifiable IIPs. Additionally, 159

instances of AE-IIPs were observed in the combined cohort, which was insufficient for the identification of individual predictive models among IIP phenotypes. Further large-scale studies are needed to establish optimal predictive models for AE-IIPs that are tailored for different ethnicities and/or IIP phenotypes.

Conclusion

The HAL score using radiographic honeycombing, age, and LDH discriminated the risk of AE-IIPs. This simple model may be helpful for the stratification of AE-IIPs risk in the clinical management of patients with IIPs.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Institutional Review Boards of Hamamatsu University School of Medicine (Hamamatsu, Japan, approval No. 20-173), Seirei Hamamatsu General Hospital (Hamamatsu, Japan, approval No. 3472), and Seirei Mikatahara General Hospital (Hamamatsu, Japan, approval No. 20-45). The requirement for informed consent was waived because of the retrospective observational design.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed in this study are available from the corresponding author upon reasonable request.

Competing interests: All authors declare no conflicts of interest in relation to this study.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions:

MK: conceptualisation, methodology, interpretation of data, writing-review and editing, and supervision, YA, TS: acquisition of data, interpretation of data, and writing-original draft, KM: analysis and interpretation of data, NY, SI: evaluation of chest imaging. SK, KY, MK, DH, YI, HY, HH, YS, KF: conceptualisation and supervision. SG: evaluation of chest imaging, conceptualisation, supervision. TF, NE, NI: conceptualisation, supervision, and writing-review and editing. TS: conceptualisation, methodology, writing-review and editing, and supervision.

Acknowledgements

We thank Ryan Chastain-Gross, Ph.D., from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Table 1. Patient characteristics

	Exploratory cohort, n=487	Validation cohort, n=402	Combined cohort, n=889
Age, years	71.0 (36-93)	70.4 (21-91)	70.8 (21-93)
Sex, male	375 (77.0)	298 (74.1)	673 (75.7)
Smoking history	341 (70.0)	270 (67.2)	611 (68.7)
Pack-year smoking	38 (1.2-200)	40 (2.0-165)	40 (1.2-200)
Dust exposure	74 (15.2)	104 (25.9)	178 (20.0)
Spirometry			
% predicted FVC, %	83.3 (24.3-141.6)	78.5 (27.6-124.1)	81.3 (24.3-141.6)
% predicted FEV_1, %	88.5 (27.0-165.5)	80.7 (31.9-131.6)	84.0 (27.0-165.5)
% predicted D_{LCO}, %[a]	75.5 (10.5-172.4)	70.2 (13.9-169.4)	73.7 (10.5-172.4)
Laboratory data			
CRP, mg/dL	0.20 (0-27.3)	0.21 (0.01-25.5)	0.20 (0-27.3)
LDH, U/L	218 (134-676)	223 (94-650)	220 (94-676)
KL-6, U/mL[b]	819 (111-7120)	789 (112-9483)	803 (111-9483)
SP-D, ng/mL[c]	184.5 (14.4-1740)	181 (17.2-1500)	182 (14.4-1740)
CT findings			
Emphysema	193 (39.6)	125 (31.1)	318 (35.8)

Honeycombing	202 (41.5)	186 (46.2)	388 (43.6)
Diagnosis of IIPs			
IPF	170 (34.9)	147 (36.6)	317 (35.7)
NSIP	35 (7.2)	20 (5.0)	55 (6.2)
COP	13 (2.7)	26 (6.4)	39 (4.4)
DIP / RB-ILD	2 (0.4)	4 (1.0)	6 (0.7)
PPFE	28 (5.7)	27 (6.7)	55 (6.2)
Unclassifiable IIPs	239 (49.1)	177 (44.0)	416 (46.8)
IPAF	48 (9.9)	39 (9.7)	87 (9.8)

Data are presented as median (range) or number (%).

COP, cryptogenic organising pneumonia; CRP, C-reactive protein; DIP, desquamative interstitial pneumonia; D_{LCO}, diffusing capacity of the lung for carbon monoxide, FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IIPs, idiopathic interstitial pneumonias; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; SP-D, pulmonary surfactant protein D

[a] D_{LCO} was evaluated in 426 and 296 patients in the exploratory and validation cohorts, respectively.

[b] KL-6 was evaluated in 486 and all patients in the exploratory and validation cohorts, respectively.

[C] SP-D was evaluated in 486 and 400 patients in the exploratory and validation cohorts, respectively.

Table 2. Fine–Gray analysis for AE-IIPs in the exploratory cohort

	Univariate		Multivariate	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age,				
>65 years (vs. ≤65)	1.17 (0.75-1.84)	0.490		
>70 years (vs. ≤70)	1.49 (1.01-2.21)	0.047		
>75 years (vs. ≤75)	1.69 (1.15-2.48)	0.008	1.65 (1.12-2.43)	0.012
>80 years (vs. ≤80)	1.56 (0.96-2.55)	0.075		
Sex, male	1.12 (0.71-1.78)	0.631		
Smoking history	1.32 (0.85-2.03)	0.222		
Dust exposure	0.95 (0.56-1.60)	0.843		
% predicted FVC				
<50% (vs. ≥50%)	1.02 (0.43-2.47)	0.961		
<60% (vs. ≥60%)	1.42 (0.86-2.35)	0.183		
<70% (vs. ≥70%)	1.47 (0.97-2.22)	0.250		
<80% (vs. ≥80%)	1.46 (0.94-2.26)	0.292		
% predicted D_{LCO}[a],				
<50% (vs. ≥50%)	1.87 (1.11-3.16)	0.020		

<60% (vs. ≥60%)	1.68 (1.09-2.59)	0.018		
<70% (vs. ≥70%)	1.47 (0.97-2.22)	0.066		
<80% (vs. ≥80%)	1.46 (0.94-2.26)	0.093		
CRP, >0.14 mg/dL	1.25 (0.84-1.85)	0.306		
LDH, >222 U/L	1.62 (1.10-2.38)	0.015	1.56 (1.06-2.31)	0.024
KL-6, >500 U/mL[b]	1.96 (1.15-3.33)	0.013		
SP-D, >110 ng/mL[c]	1.75 (1.04-2.86)	0.035		
Emphysema	1.52 (1.04-2.23)	0.032		
Honeycombing	1.67 (1.14-2.45)	0.009	1.64 (1.11-2.42)	0.012
IPAF	0.90 (0.46-1.78)	0.772		

Variables in multivariate analysis were selected by *p*-value-based stepwise selection.

Other candidate multivariate models are shown in Supplementary Table 1.

[a] Evaluated in 426 patients who underwent assessment of D_{LCO}

[b] Evaluated in 486 patients who underwent assessment of serum KL-6.

[c] Evaluated in 486 patients who underwent assessment of serum SP-D

Table 3. Cumulative incidence rate for AE-IIPs

	Exploratory cohort		Validation cohort		Combined cohort	
	Predicted	Observed	Predicted	Observed	Predicted	Observed
C-index	0.62 (0.56-0.67)		0.67 (0.60-0.73)		0.63 (0.59-0.67)	
1-year AE-IIPs rate, %						
Score 0	2.3	1.8	1.3	0	1.9	1.1
Score 1	5.4	6.2	3.7	4.4	4.7	5.4
Score ≥2	8.5	7.7	7.0	7.6	8.0	7.6
2-year AE-IIPs rate, %						
Score 0	4.0	4.9	2.8	1.3	3.5	3.4
Score 1	9.5	9.4	6.7	7.3	8.3	8.5

Score ≥2	14.3	14.1	13.8	14.4	14.2	14.2
3-year AE-IIPs rate, %						
Score 0	5.7	7.1	4.0	2.9	5.1	5.3
Score 1	14.0	13.7	9.5	8.9	12.0	11.6
Score ≥2	20.9	21.0	18.4	19.9	19.7	20.5
5-year AE-IIPs rate, %						
Score 0	8.9	9.7	5.8	2.9	7.7	6.9
Score 1	20.3	20.7	13.3	11.8	17.7	17.1
Score ≥2	30.8	30.7	25.4	29.7	28.7	30.3
10-year AE-IIPs rate, %						
Score 0	15.2	16.6	9.2	14.3	12.9	14.9

Score 1	33.2	32.9	20.8	21.7	28.4	28.7
Score ≥2	44.5	47.6	38.0	29.7	43.0	43.1

Table 4. Time-dependent positive predictive value and negative predictive value of the HAL score

	Exploratory cohort		Validation cohort		Combined cohort	
	tdPPV	tdNPV	tdPPV	tdNPV	tdPPV	tdNPV
1-year						
Score ≥1 (vs. <1)	6.8	98.1	5.9	100	6.4	98.9
Score ≥2 (vs. <2)	7.7	95.3	7.7	97.1	7.6	96.0
2-year						
Score ≥1 (vs. <1)	11.4	95.1	10.1	98.6	10.8	96.6
Score ≥2 (vs. <2)	14.2	92.1	13.2	94.6	13.7	93.2
3-year						
Score ≥1 (vs. <1)	16.9	93.1	14.0	97.1	15.6	94.8

Score ≥2 (vs. <2)	21.5	88.7	20.0	93.1	20.8	90.6
5-year						
Score ≥1 (vs. <1)	25.1	90.4	19.8	97.0	22.9	93.1
Score ≥2 (vs. <2)	31.0	83.2	29.5	91.1	30.2	86.3
10-year						
Score ≥1 (vs. <1)	37.3	80.8	25.9	84.6	33.4	82.7
Score ≥2 (vs. <2)	48.4	72.8	37.7	81.8	45.1	76.3

Data are expressed as percentage.
tdNPV, time-dependent negative predictive value; tdPPV, time-dependent positive predictive value

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Figure legends

Figure 1. Flow diagram of study patients

IIPs, idiopathic interstitial pneumonias

Figure 2. A predictive model for acute exacerbation of idiopathic interstitial pneumonias

a) HAL score, which was composed of honeycombing (H), age >75 years (A), and lactate dehydrogenase (LDH) level >222 U/L (L). Cumulative incidence of acute exacerbation of idiopathic interstitial pneumonias b) in the exploratory cohort, c) validation cohort, and d) combined cohort.

Blue, green, and red lines indicate HAL scores of 0, 1, and ≥2, respectively.

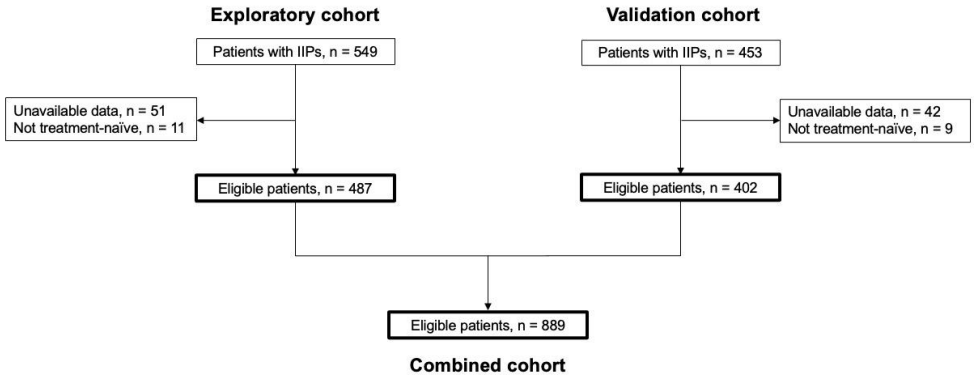
Figure 3. Subgroup analysis

Cumulative incidence of acute exacerbation of idiopathic interstitial pneumonias a) in patients with idiopathic pulmonary fibrosis (IPF group) and b) without idiopathic pulmonary fibrosis (non-IPF group), and c) in patients who received antifibrotic agents during the observation period (antifibrotic group) and d) who did not receive antifibrotic agents (non-antifibrotic group). Blue, green, and red lines indicate HAL scores of 0, 1, and ≥2, respectively.

Figure 4. Overall survival

Overall survival according to the HAL score.

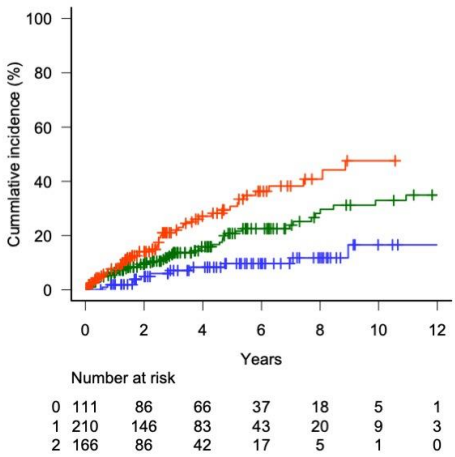
Blue, green, and red lines indicate HAL scores of 0, 1, and ≥2, respectively.


Exploratory cohort
Patients with IIPs, n = 549
Unavailable data, n = 51
Not treatment-naïve, n = 11
Eligible patients, n = 487
Validation cohort
Patients with IIPs, n = 453
Unavailable data, n = 42
Not treatment-naïve, n = 9
Eligible patients, n = 402
Eligible patients, n = 889
Combined cohort

a)

HAL score	Point
Honeycombing (H)	1
Age >75 years (A)	1
LDH >222 U/L (L)	1
Total points	3

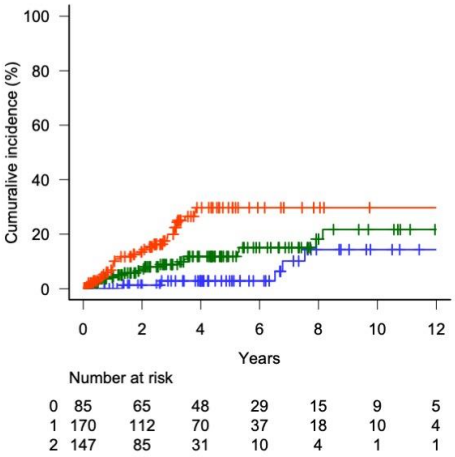
b)



Number at risk

0	111	86	66	37	18	5	1
1	210	146	83	43	20	9	3
2	166	86	42	17	5	1	0

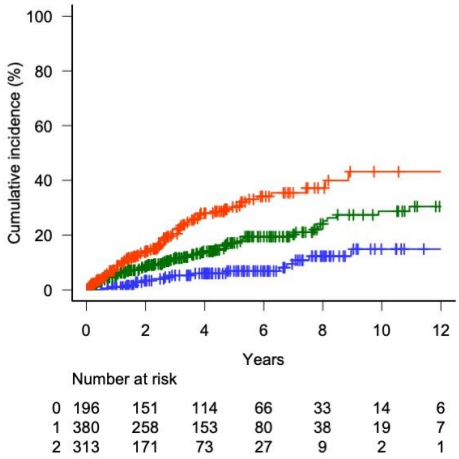
c)



Number at risk

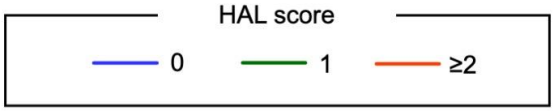
0	85	65	48	29	15	9	5
1	170	112	70	37	18	10	4
2	147	85	31	10	4	1	1

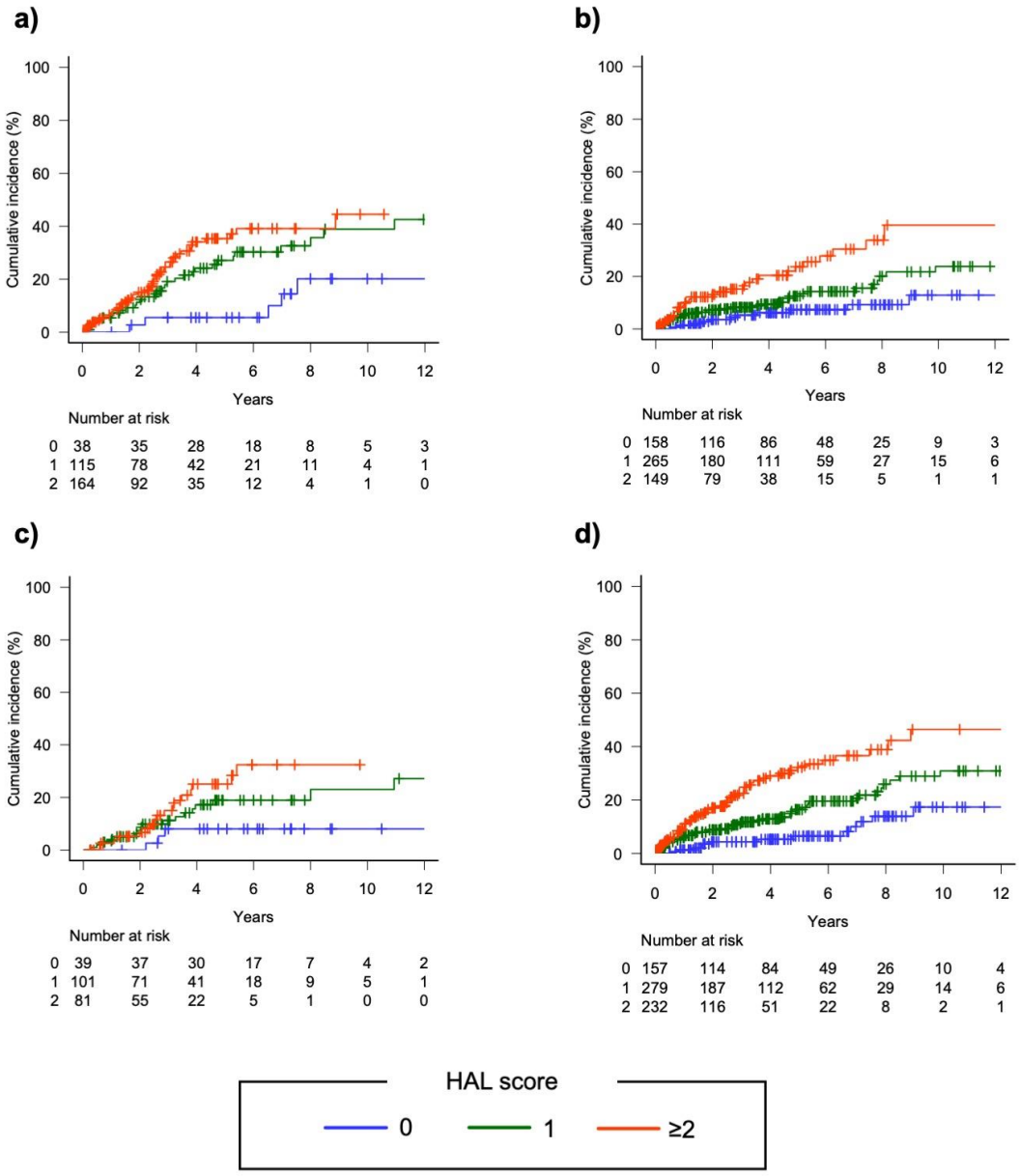
d)

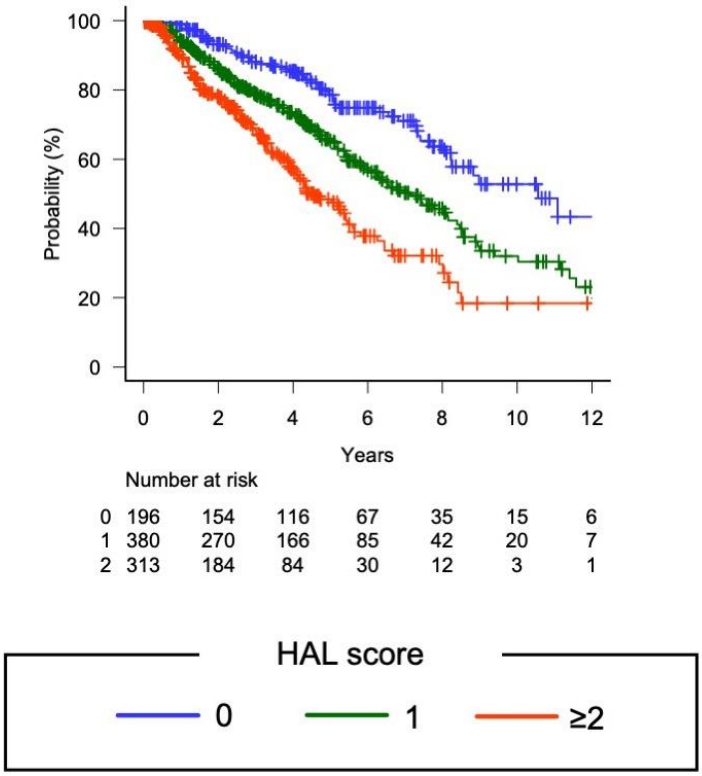


Number at risk

0	196	151	114	66	33	14	6
1	380	258	153	80	38	19	7
2	313	171	73	27	9	2	1




a)
Cumulative incidence (%)
100
80
60
40
20
0
0 2 4 6 8 10 12
Years
Number at risk
0 38 35 28 18 8 5 3
1 115 78 42 21 11 4 1
2 164 92 35 12 4 1 0
b)
Cumulative incidence (%)
100
80
60
40
20
0
0 2 4 6 8 10 12
Years
Number at risk
0 158 116 86 48 25 9 3
1 265 180 111 59 27 15 6
2 149 79 38 15 5 1 1
c)
Cumulative incidence (%)
100
80
60
40
20
0
0 2 4 6 8 10 12
Years
Number at risk
0 39 37 30 17 7 4 2
1 101 71 41 18 9 5 1
2 81 55 22 5 1 0 0
d)
Cumulative incidence (%)
100
80
60
40
20
0
0 2 4 6 8 10 12
Years
Number at risk
0 157 114 84 49 26 10 4
1 279 187 112 62 29 14 6
2 232 116 51 22 8 2 1
HAL score
0
1
≥2


100
80
60
40
20
0
Probability (%)
0
2
4
6
8
10
12
Years
Number at risk
0 196 154 116 67 35 15 6
1 380 270 166 85 42 20 7
2 313 184 84 30 12 3 1
HAL score
0
1
≥2

A predictive model for acute exacerbation of idiopathic interstitial pneumonias

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Supplementary Methods

Data collection:

The following laboratory data and pulmonary function were collected at the time of IIP diagnosis: levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), Krebs von Lungen-6 (KL-6), surfactant protein D (SP-D), percent predicted forced vital capacity (%FVC), percent predicted forced expiratory volume in 1 s (%FEV_1), and diffusing capacity of the lung for carbon monoxide (D_{LCO}).

The presence of emphysema and honeycombing was evaluated by two experienced radiologists (S.I., with 15 years of experience, and N.Y., with 20 years of experience) who were blinded to all other patient data. Emphysema was defined as focal areas or regions of low attenuation without visible walls, and honeycombing was defined as clustered cystic air spaces, typically 3–10 mm in diameter with walls 1–3 mm in thickness, typically in subpleural regions, based on the Fleischner Society guidelines (Hansell DM et al. Fleischner Society: Glossary of terms for thoracic imaging. *Radiology* 2008; 246: 697–722.). Disagreements concerning the presence of emphysema and honeycombing were resolved by consensus decision in collaboration with a third radiologist (S.G., with 22 years of experience).

During the study period, treatments, the occurrence of AE-IIPs, and outcomes of IIPs were recorded. The definition of AE-IIPs was defined as acute respiratory deterioration (with a duration typically less than 1 month) accompanied by new widespread alveolar abnormalities (bilateral ground-glass opacity and/or consolidation), in the absence of an alternative explanation such as cardiac failure or fluid overload (Collard HR et al. Acute exacerbation of idiopathic pulmonary fibrosis an international working group report. *Am. J. Respir. Crit. Care Med.* 2016; 194: 265–275.).

Statistical analysis:

Student's *t*-test and Fisher's exact test were used for comparisons of continuous and categorical variables, respectively. Pearson's correlation analysis was used to assess correlations among clinical factors. Interobserver reproducibilities for HRCT imaging features were evaluated using the κ statistic. The Kaplan–Meier method and the log-rank test were used to analyse overall survival. Data were expressed as the median (range) or number (%), unless otherwise indicated. All statistical tests were two-sided, and $p < 0.05$ was considered indicative of statistical significance. All values were analysed using R 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria) with "tidyverse" packages. Following optional packages were used: boot (ver.1.3-28; Canty A, et al., 2021), survival (ver.3.2-13; Therneau TM, 2021), timeROC (ver.0.4; Blanche P, et al., 2019).

Supplementary Table 1. Results of multivariate Fine-Gray analysis for acute exacerbation in the exploratory cohort: other combinations not shown in Table 2.

	Set A		Set B		Set C	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, >75 years (vs. ≤75)	1.57 (1.02-2.42)	0.041	1.61 (1.06-2.44)	0.027		
% predicted D_{LCO}, <50% (vs. ≥50%)	1.33 (0.76-2.32)	0.310				
LDH, >222 U/L	1.57 (1.02-2.41)	0.040	1.69 (1.11-2.57)	0.014	1.58 (1.07-2.33)	0.021
KL-6, >500 U/mL	1.20 (0.66-2.18)	0.540				
SP-D, >110 ng/mL	1.82 (1.01-3.28)	0.047	1.90 (1.08-3.36)	0.027		
Emphysema	1.35 (0.89-2.05)	0.160	1.43 (0.94-2.15)	0.091		
Honeycombing	1.63 (1.08-2.48)	0.021	1.70 (1.13-2.56)	0.011	1.67 (1.14-2.45)	0.009

Set A consists of all variables that had p <0.100 in univariate analysis. Set B and C consists of variables selected by stepwise selection using AIC and BIC, respectively. When cut-off values of age ≥70 or ≥80 years were employed (instead of ≥75 years), age was not selected as the significant predictive factors. Likewise, when cut-off values of % predicted D_{LCO} <60%, <70% or <80% were employed (instead of <50%), % predicted D_{LCO} was not selected as the significant predictive factors.

Supplementary Table 2. Predictive accuracy for AE-IIPs of IPF and non-IPF in the combined cohort

	IPF		Non-IPF	
	Predicted	Observed	Predicted	Observed
C-index	0.59 (0.54-0.65)		0.63 (0.57-0.69)	
1-year AE-IIPs rate, %				
Score 0	N.E.	0	2.3	1.3
Score 1	5.0	5.4	4.8	5.5
Score ≥2	6.3	6.5	8.6	9.0
2-year AE-IIPs rate, %				
Score 0	3.6	2.7	3.5	3.6
Score 1	11.6	11.2	7.0	7.2
Score ≥2	14.4	15.0	13.2	13.1
3-year AE-IIPs rate, %				
Score 0	7.3	5.5	4.3	5.3
Score 1	19.3	19.1	8.6	8.2
Score ≥2	23.2	24.5	15.7	15.2
5-year AE-IIPs rate, %				
Score 0	10.5	5.5	6.6	7.3
Score 1	27.4	27.0	13.1	12.5
Score ≥2	32.5	35.4	23.3	23.7
10-year AE-IIPs rate, %				
Score 0	16.2	20.1	11.5	12.9
Score 1	39.0	38.9	23.5	23.8
Score ≥2	46.5	44.5	36.2	39.6

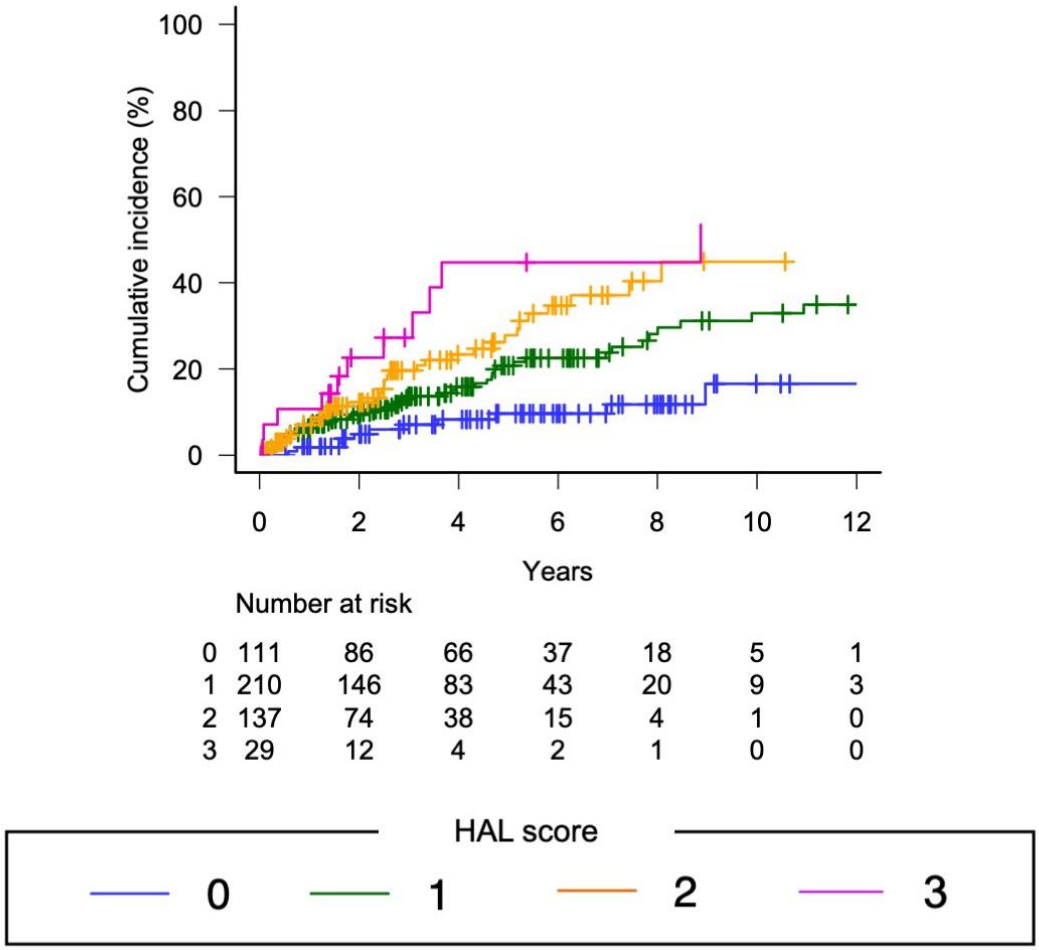
AE, acute exacerbation; IPF, idiopathic pulmonary fibrosis; N.E.. not estimable

Supplementary Table 3. Predictive accuracy for overall survival of IIPs in the combined cohort

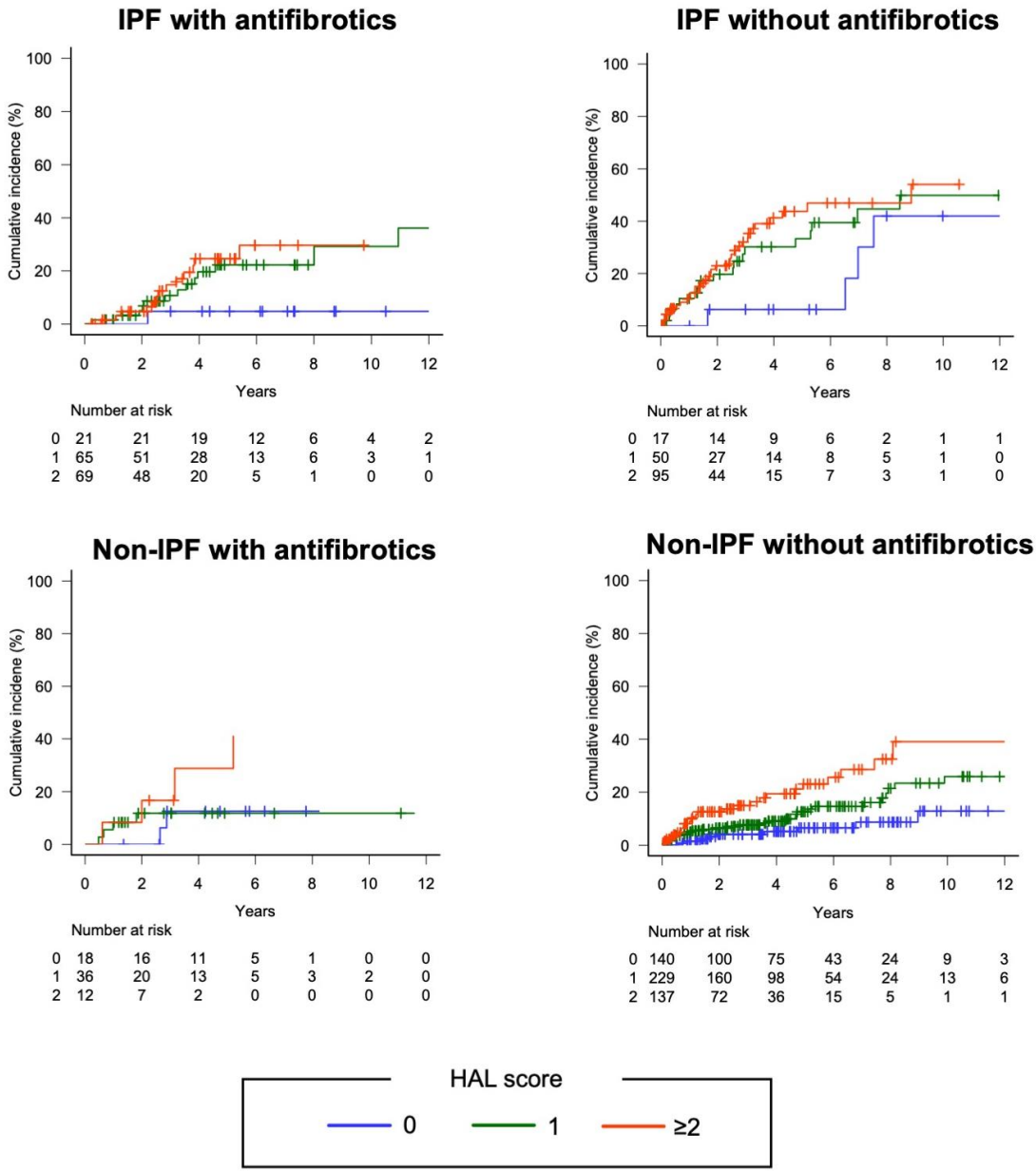
	Predicted	Observed
C-index	0.61 (0.58-0.64)	
1-year OS rate, %		
Score 0	97.0	98.9
Score 1	94.4	94.2
Score ≥2	90.8	89.7
2-year OS rate, %		
Score 0	92.3	93.2
Score 1	86.4	86.3
Score ≥2	78.4	78.1
3-year OS rate, %		
Score 0	88.0	88.1
Score 1	79.1	78.8
Score ≥2	67.9	68.5
5-year OS rate, %		
Score 0	79.0	78.6
Score 1	65.2	65.9
Score ≥2	49.2	48.5
10-year OS rate, %		
Score 0	54.0	52.8
Score 1	32.3	32.0
Score ≥2	15.4	18.4

OS, overall survival

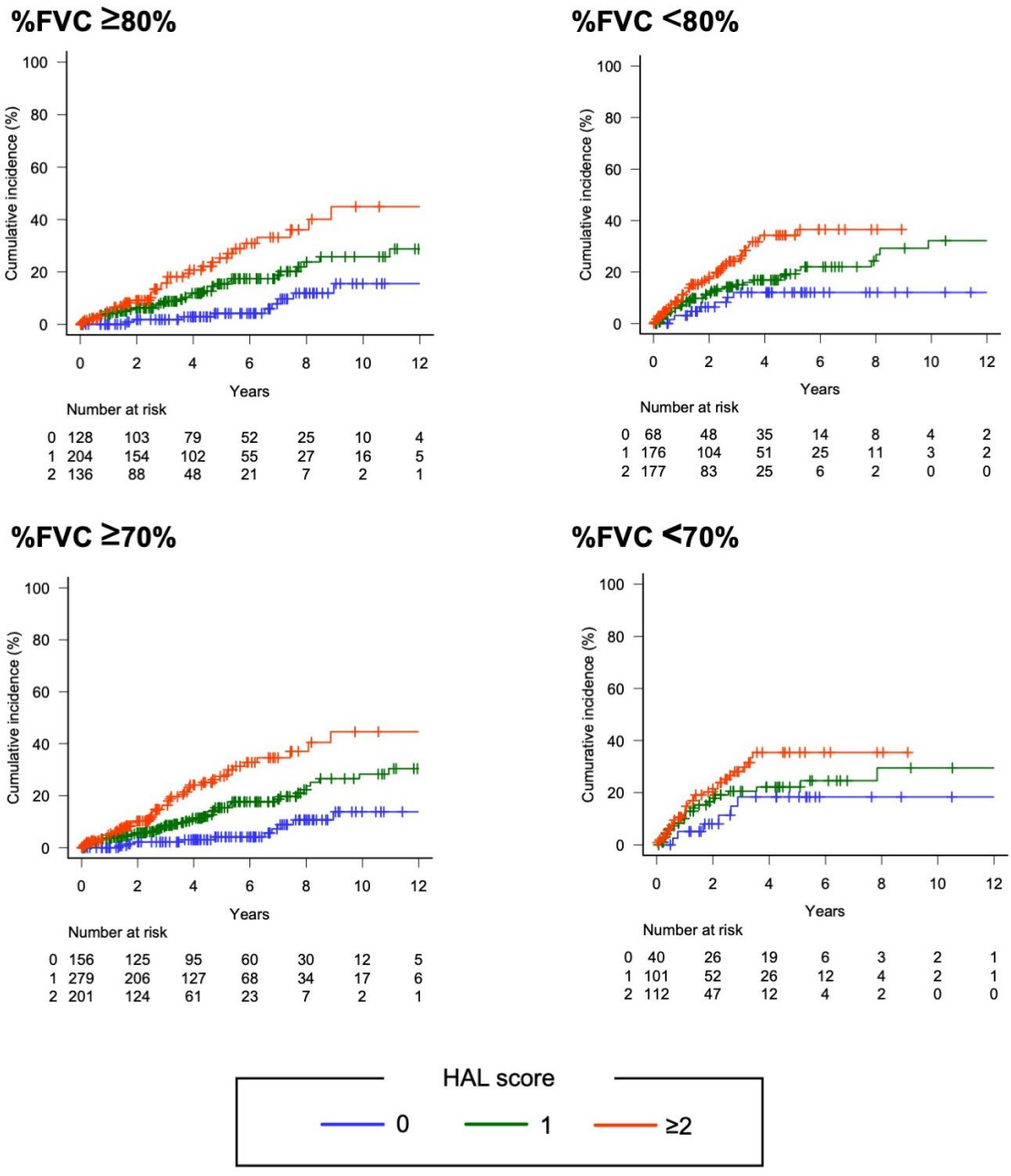
Supplementary Figure 1. Cumulative incidence AE-ILD according to the prediction score



Supplementary Figure 2. Influence of antifibrotics on patients with and without idiopathic pulmonary fibrosis.



Supplementary Figure 3. Subgroup analysis of HAL score divided by levels of %FVC



Supplementary Figure 4. Subgroup analysis of HAL score in patients with the CT images with a slice thickness from 1.0 mm to ≤1.5 mm.