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

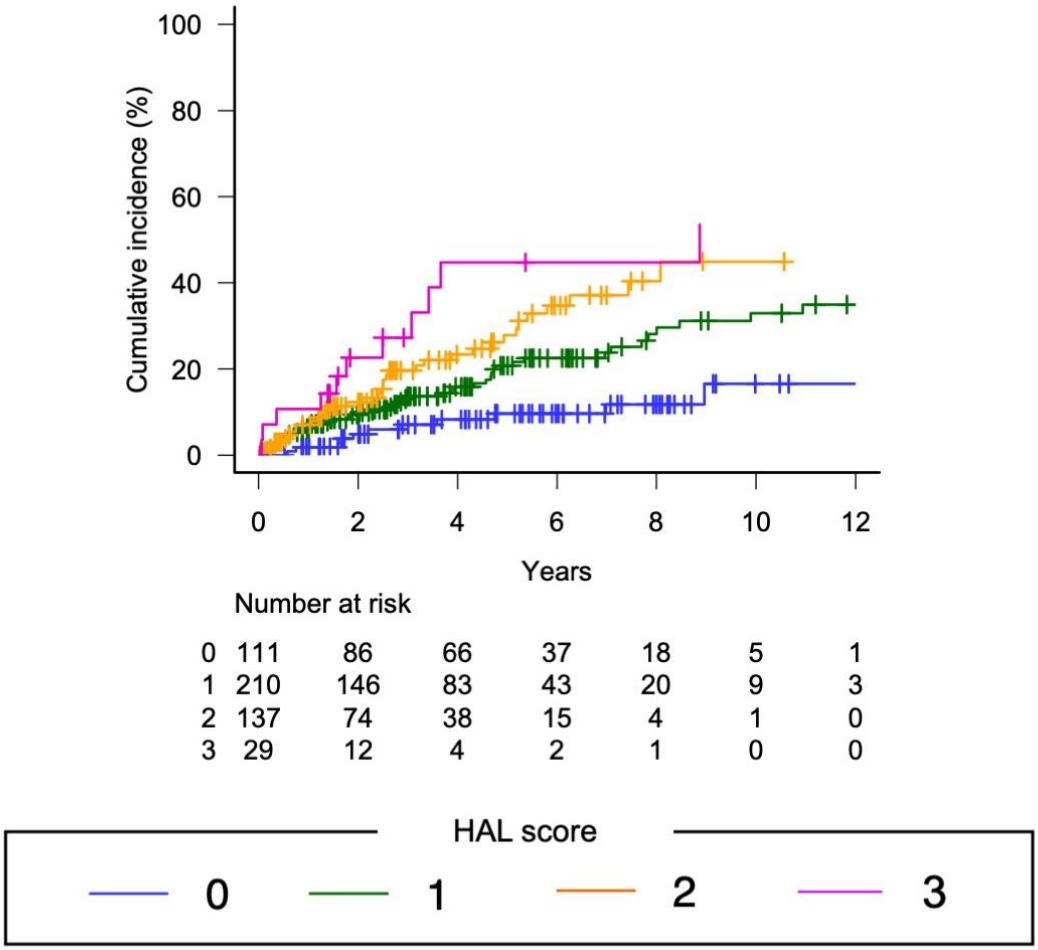
AE, acute exacerbation; IPF, idiopathic pulmonary fibrosis; N.E.. not estimable

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

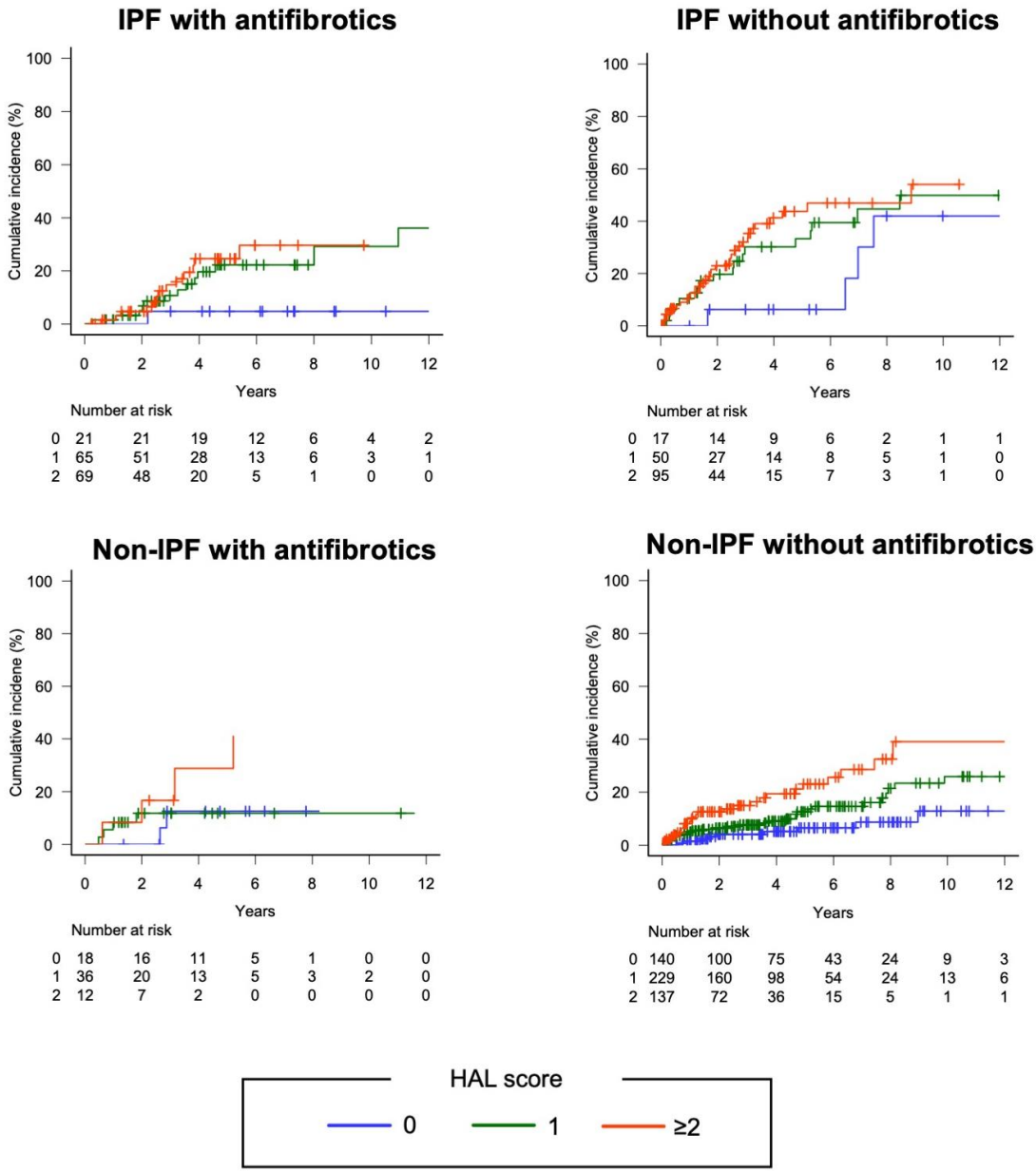
	Predicted	Observed
C-index	0.61 (0.58-0.64)	
1-year OS rate, %		
Score 0	97.0	98.9
Score 1	94.4	94.2
Score ≥2	90.8	89.7
2-year OS rate, %		
Score 0	92.3	93.2
Score 1	86.4	86.3
Score ≥2	78.4	78.1
3-year OS rate, %		
Score 0	88.0	88.1
Score 1	79.1	78.8
Score ≥2	67.9	68.5
5-year OS rate, %		
Score 0	79.0	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

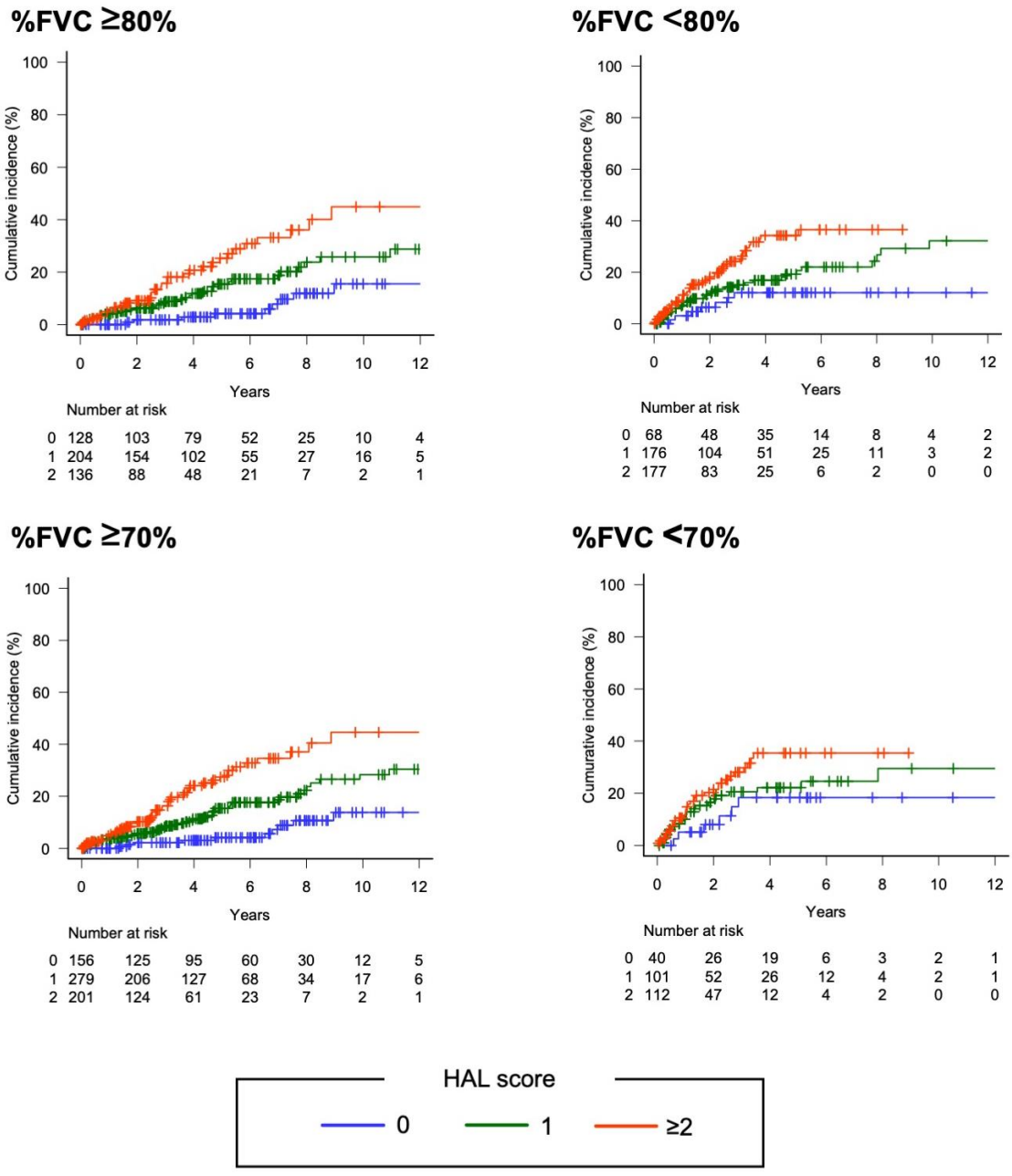
Supplementary Figure 1. Cumulative incidence AE-ILD according to the prediction score



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.