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Prognostic value of a composite physiologic index developed by adding bronchial and hyperlucent volumes quantified via artificial intelligence technology

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Abstract

Background The composite physiologic index (CPI) was developed to estimate the extent of interstitial lung disease (ILD) in idiopathic pulmonary fibrosis (IPF) patients based on pulmonary function tests (PFTs). The CALIPER-revised version of the CPI (CALIPER-CPI) was also developed to estimate the volume fraction of ILD measured by CALIPER, an automated quantitative CT postprocessing software. Recently, artificial intelligence-based quantitative CT image analysis software (AIQCT), which can be used to quantify the bronchial volume separately from the ILD volume, was developed and validated in IPF. The aim of this study was to develop AIQCT-derived CPI formulas to quantify CT abnormalities in IPF and to investigate the associations of these CPI formulas with survival.

Methods The first cohort included 116 patients with IPF. In this cohort, ILD, bronchial, and hyperlucent volumes on CT were quantified using AIQCT. New CPI formulas were developed based on PFTs to estimate the volume fraction of ILD (ILD-CPI), the sum of the ILD and bronchial volume fractions (ILDB-CPI), and the sum of the ILD, bronchial and hyperlucent volume fractions (ILDBH-CPI). The associations of the original CPI, the CALIPER-CPI and the AIQCT-derived CPIs with survival were analyzed in the first cohort and in a second cohort of patients with IPF ($n=72$).

Results In the first cohort, over a median observation time of 92.8 months, 79 patients (68.1%) died, and one patient (0.9%) underwent living-donor lung transplantation. The original CPI, the CALIPER-CPI, and all AIQCT-derived CPIs were associated with overall survival (hazard ratios: 1.07–1.22). The C-index of the ILDB-CPI (0.759) was the highest among all AIQCT-derived CPIs and was comparable to that of the original CPI (0.765) and the CALIPER-CPI (0.749). The C-index of the ILDBH-CPI (0.729) was lower than that of the other CPI variables. The second cohort yielded similar C-indices as the first cohort for the original CPI (0.738), CALIPER-CPI (0.757) and ILDB-CPI (0.749).

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Conclusions The ILDB-CPI can predict the outcomes of IPF patients with a similar performance to that of the original CPI and the CALIPER-CPI. Adding the hyperlucent volume to the CPI formula did not improve its predictive accuracy for mortality.

Trial registration None (no health care interventions were performed).

Keywords Artificial intelligence-based quantitative computed tomographic image analysis software, Composite physiologic index, Idiopathic pulmonary fibrosis, Interstitial lung disease, Bronchial volume, Hyperlucent volume

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease (ILD) of unknown origin with a median survival time of approximately 3 years after diagnosis [1, 2]. The severity of IPF is evaluated by assessing restriction and diffusion impairments on pulmonary function tests (PFTs) as well as by the extent of abnormalities detected on computed tomography (CT); both of these factors are associated with disease prognosis [3–5]. Although certain PFT parameters are correlated with the extent of abnormalities detected on CT, the presence of emphysema often confounds the interpretation of these PFTs [6–8].

The composite physiologic index (CPI) was developed to estimate the extent of ILD on CT in IPF patients on the basis of PFT parameters. The CPI represents the functional defects derived from pulmonary fibrosis while excluding the influences of coexistent emphysema by integrating three PFT parameters: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and diffusing capacity for carbon monoxide (DLCO) [8]. Compared with the individual PFT parameters, the CPI is a more accurate predictor of mortality in patients with IPF [8, 9].

The original version of the CPI was constructed on the basis of disease extent, which was visually assessed on CT [8]. Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) is an automated quantitative CT postprocessing software that can be used to quantify the total volume fraction of ILD [10]. CALIPER has been validated in IPF and found to be comparable or superior to visual scoring in terms of functional correlations between the volume fraction of ILD on CT and the results of PFTs [10]. The CALIPER-revised version of the CPI (CALIPER-CPI) was developed based on the volume fraction of ILD, which was measured by CALIPER; PFT parameters were used as independent variables [10]. The CALIPER-CPI was shown to match or surpass the original CPI in predicting mortality in IPF [11].

AIQCT is an artificial intelligence-based quantitative CT image analysis software that we recently developed, validated, and applied for the cross-sectional evaluation of patients with IPF [12]. AIQCT can be used to label ground-glass opacities (GGOs), reticulation, honeycombing, the bronchi in the lung field, hyperlucent areas (mostly corresponding to emphysema) and other CT abnormalities as distinct lesions in an automated and reproducible manner. AIQCT can quantify not only the ILD volume but also the bronchial and hyperlucent volumes, which can influence pulmonary function and outcomes in IPF. The detection of traction bronchiectasis on CT is related to fibrosis [13] and is included in the definition of fibrotic ILD in the inclusion criteria of the INBUILD trial [14]. The sum of the ILD and bronchial volumes may be more strongly associated with survival than the ILD volume alone. In patients with combined pulmonary fibrosis and emphysema (CPFE), survival may be related to the percentage of the sum of the fibrosis and emphysema volumes relative to the total lung volume [15]; however, the effect of adding the hyperlucent volume to the ILD volume on the association with prognosis remains poorly understood. We hypothesized that the CPI formula could be refined with the AIQCT-assessed ILD volume fraction and other measurements.

The aim of this study was to develop AIQCT-derived CPI formulas on the basis of the quantification of CT abnormalities in IPF. We quantified the volume fraction of ILD abnormalities and hyperlucent and bronchial volume fractions with AIQCT, investigated the associations of AIQCT measurements with PFT parameters, and constructed CPI formulas to calculate the volume fraction of composite CT patterns based on PFTs in a Japanese cohort of patients with IPF (the first cohort). We tested the predictive accuracy of the AIQCT-derived CPIs for survival in a second, independent cohort and compared it with that of the original CPI and the CALIPER-derived CPI.

Methods

Study patients

The first cohort comprised 116 patients with IPF who underwent high-resolution CT (HRCT) and PFTs (including measurement of DLCO) within a period of 3 months at Kyoto University Hospital between April 2011 and December 2019. The diagnosis of IPF was based on previously reported guidelines [5, 16]. Patients were excluded if they had an acute exacerbation of IPF or other respiratory diseases that could influence pulmonary function and CT data at baseline. All patients in the first cohort were enrolled in our previous study [12].

The second cohort comprised 72 treatment-naïve patients with IPF who underwent PFTs at Tenri Hospital between December 2004 and October 2008 and at Kyoto University Hospital between December 2007 and August 2009. The second cohort was independent of the first cohort.

CONSORT diagrams of the first and second cohorts are shown in Figure S1.

The Institutional Review Board of Kyoto University and the Ethics Committee of Tenri Hospital approved this study (approval numbers R1353, E2119 and No. 635, respectively). The requirement for written informed consent was waived due to the retrospective nature of this study. This study was conducted in accordance with the amended Declaration of Helsinki.

Clinical data collection and PFTs

The following clinical data were collected from the medical records of the patients: age, sex, smoking history, and treatment history. Antifibrotic drug use was defined as the use of pirfenidone ≥ 1200 mg/day or nintedanib ≥ 200 mg/day for three or more months. Previously published equations for adults were used to determine the predicted values of the PFT parameters (FVC, FEV_1 and DLCO) [17–19].

Quantification of HRCT

The steps carried out in this research are shown in Fig. 1. All patients in the first cohort underwent thin-section CT examinations in the supine position at full inspiration. No contrast medium was used. Details about the HRCT techniques used were described in a previous report [12]. AIQCT can be used to automatically detect and quantify each of eight parenchymal patterns (normal lungs, GGOs, reticulation, consolidation, honeycombing, nodules, interlobular septum and hyperlucencies), lung vessels and bronchi. In the development of the AIQCT software, the final label "hyperlucency" was derived from the original labels "hyperlucency", "cyst", "centrilobular emphysema", "panlobular emphysema", "cavity surrounded by infiltration", and "cavity surrounded by mass", thus suggesting that "hyperlucent" regions mostly correspond to emphysema [12]. The ILD volume was defined as the sum of the volumes of GGOs, reticulation, and honeycombing. All measurements are expressed as a percentage of the total lung volume. All the results of AIQCT lung parenchymal segmentation were visually reviewed by two independent observers (M.U. and T.H.) to confirm the validity of the automated CT image analysis.

Statistical analysis

Demographic, PFT, AIQCT and therapeutic variables are expressed as medians (IQRs, interquartile ranges) or numbers (percentages), as appropriate. Univariate linear regression analysis was used to evaluate the associations of the AIQCT measurements with PFT variables. Multiple regression models for predicting the AIQCT variables were constructed using the same three PFT parameters [the percentage of predicted FVC (%FVC), $\%FEV_1$, and %DLCO] as in the original CPI formula. The backward selection method with a cutoff value of $P < 0.05$ was used to develop the predictive formulas for the AIQCT variables. The predictive formulas were as follows: ILD-CPI, reflecting the AIQCT-assessed ILD volume fraction; ILDB-CPI, reflecting the sum of the ILD and bronchial volume fractions; and ILDBH-CPI, reflecting the sum of the ILD, bronchial and hyperlucent volume fractions.

The survival time was calculated as the duration between the date of the baseline PFT and patient death. Patients were right-censored at the time of transplantation or last contact until January 31, 2023, in the first cohort, and until September 30, 2014, in the second cohort. Both living-donor lobar lung transplantation and patient death were treated as an event. The median observation time was calculated with the reverse Kaplan–Meier estimator [20]. A Cox proportional hazards regression model and the concordance index (Harrell's C-index) were used to evaluate and compare the predictive accuracy of the CPI variables (the original CPI, the CALIPER-CPI, and the AIQCT-derived CPIs) for overall survival [21, 22]. The first and second cohorts were divided into two groups on the basis of the cutoff values of the CPI variables, determined by performing time-dependent receiver operating characteristic (ROC) curve analysis for 24-month survival [23, 24]; then, Kaplan–Meier survival analysis was used to estimate survival time. The log-rank test was used to compare survival between the two groups.

All data analyses were performed via R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The baseline characteristics of the study patients in the first cohort are summarized in Table 1. Over the median observation time of 92.8 months (95% confidence interval: 72.2, 112.6), 79 patients (68.1%) died, and one patient (0.9%) underwent living-donor lung transplantation.

Relationships between AIQCT variables and PFT parameters

The associations of AIQCT variables with PFT parameters and CPIs (the original CPI and the CALIPER-CPI) are shown in Additional File: Table S1. The AIQCT-assessed ILD volume fraction was moderately correlated with all PFT parameters (Pearson's correlation coefficient: 0.36–0.68). The hyperlucent volume fractions were

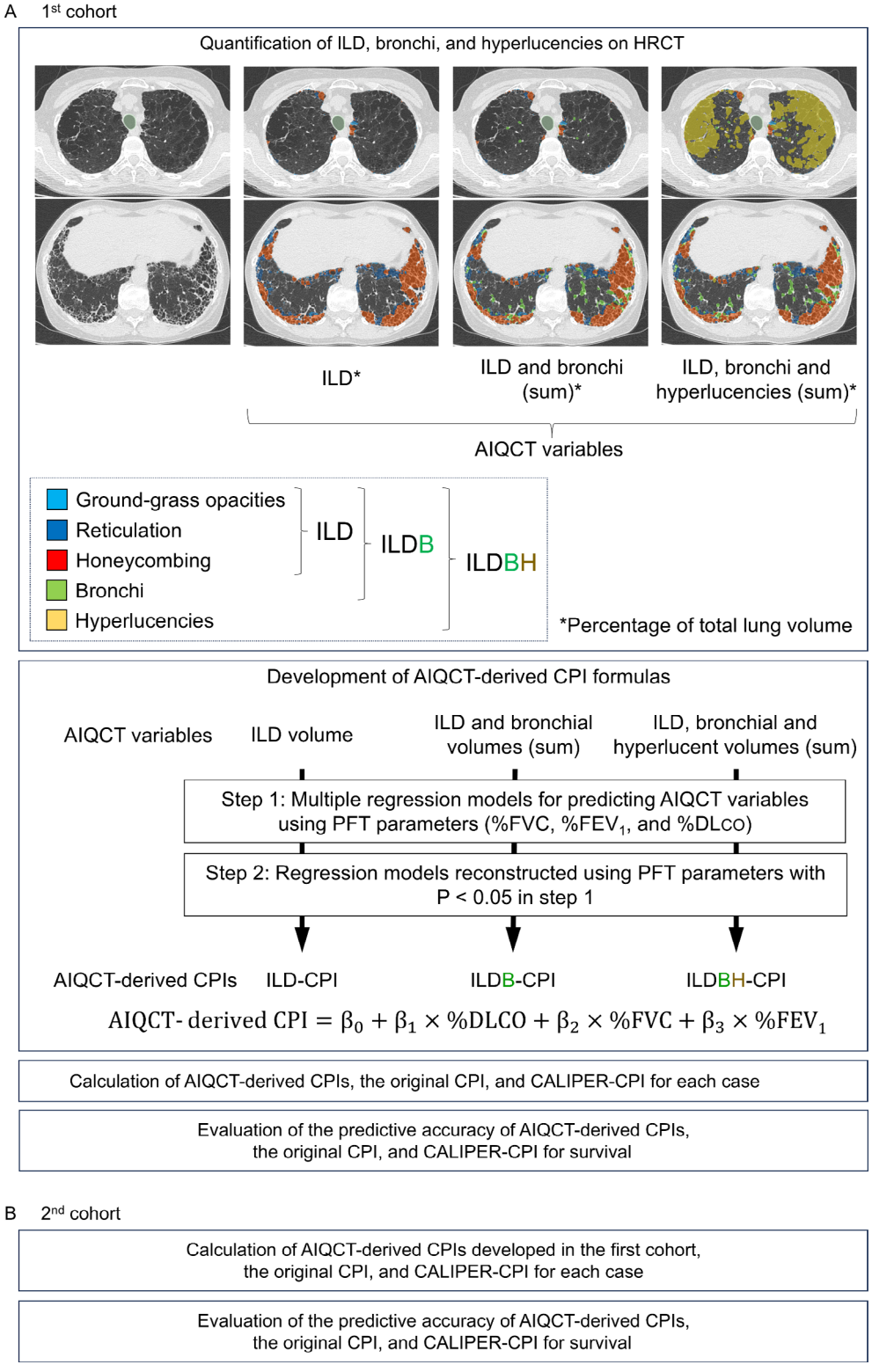

Fig. 1 Study overview for the first and second cohorts. Representative HRCT scans and overlayed images with ground–glass opacities, reticulation, honeycombing, bronchi, and hyperlucencies colored by AIQCT are shown in the subsection *Quantification of ILD, bronchi, and hyperlucencies on HRCT*. ILD, interstitial lung disease; HRCT, high-resolution computed tomography; AIQCT, artificial intelligence-based quantitative computed tomographic image analysis software; ILDB, interstitial lung disease and bronchial volumes; ILDBH, interstitial lung disease, bronchial and hyperlucent volumes; PFT, pulmonary function test; %FVC, percentage of predicted forced vital capacity; $\%FEV_1$, percentage of predicted forced expiratory volume in one second; %DLCO, percentage of predicted diffusing capacity for carbon monoxide; CPI, composite physiologic index

Table 1 Patient characteristics in the first cohort and the second cohort

	1st cohort		2nd cohort	
Number	116		72	
Age, median (IQR)	71.5	(65.5, 77)	68	(63, 73)
Male, *n* (%)	106	(91.4)	58	(80.6)
Ever smoked, *n* (%)	107	(92.2)	55	(76.4)
Brickman index, median	800	(455, 1200)	NA	NA
%FVC, median (IQR)	83.1	(70.8, 94.7)	77.5	(63.3, 91.2)
%FEV_1, median (IQR)	88.5	(78.3, 97.1)	80.4	(69.1, 97.1)
%DLCO, median (IQR)	48.5	(38.7, 61.8)	42.6	(33.3 56.7)
The original CPI, median (IQR)	43.9	(35.3, 53.1)	49.9	(41.8, 57.7)
CALIPER-CPI, median (IQR)	15.6	(7.1, 22.9)	20.4	(10.2, 27.5)
AIQCT measurements				
ILD, %, median (IQR)	9.2	(5.9, 13.7)	NA	NA
Bronchi, %, median (IQR)	4.0	(3.2, 5.0)	NA	NA
Hyperlucencies, %, median (IQR)	1.1	(0.1, 4.1)	NA	NA
ILD and bronchi (sum), %, median (IQR)	13.2	(9.6, 19.3)	NA	NA
ILD, bronchi and hyperlucencies (sum), %, median (IQR)	16.9	(11.2, 24.1)	NA	NA
Treatment				
Antifibrotic agent at baseline, *n* (%)	12	(10.3)	0	(0.0)
Antifibrotic agent during the observational time, *n* (%)	62	(53.4)	10	(13.9)
Long-term oxygen therapy at baseline, *n* (%)	10	(8.6)	NA	NA

IQR, interquartile range; NA, not available; %FVC, the percentage of predicted forced vital capacity; %FEV_1, the percentage of predicted forced expiratory volume in one second; %DLCO, the percentage of predicted diffusing capacity for carbon monoxide; CPI, composite physiologic index; CALIPER, Computer-Aided Lung Informatics for Pathology Evaluation and Rating; AIQCT, artificial intelligence-based quantitative computed tomographic image analysis software; ILD, interstitial lung disease

positively correlated with %FVC, negatively correlated with %DLCO, and not correlated with %FEV_1, the original CPI or the CALIPER-CPI.

Table 2 shows the results of the multiple linear regression models for predicting the AIQCT variables using the PFT parameters (%FVC, %FEV_1, and %DLCO) as the original CPI and the results of linear regression models that were conducted with the backward method. The AIQCT-derived CPIs developed from the regression equations are shown in Table 3.

Associations of AIQCT-derived CPIs with survival

The associations between the CPI variables (the original CPI, CALIPER-CPI, and AIQCT-derived CPIs) and overall survival in the first cohort are shown in Table 4a. The original CPI, the CALIPER-CPI, and all AIQCT-derived CPIs were associated with overall survival. The ILDB-CPI had the highest C-index among the AIQCT-derived CPIs, and it was comparable to the C-index of the CALIPER-CPI and the original CPI. The C-index of the ILDBH-CPI was lower than that of the other CPI variables, especially the original CPI ($P=0.01$).

Time-dependent ROC curve analyses based on the original CPI, the CALIPER-CPI, and the ILDB-CPI are shown in Additional File: Table S2, and the corresponding ROC curves are shown in Additional File: Figure S2. The Kaplan–Meier survival curves for the original CPI, the CALIPER-CPI, and the ILDB-CPI are shown in Fig. 2A-C. Analysis of these survival curves revealed distinct differences in overall survival between groups when any of the CPI formulas were used.

Evaluation of the predictive accuracy of the AIQCT-derived CPIs for survival in the second cohort

The baseline characteristics of the study patients in the second cohort are summarized in Table 1. Over the median observation time of 82.4 months (95% confidence interval: 66.9, 91.2), 40 patients (55.6%) died, and one (1.4%) underwent deceased-donor lung transplantation.

The associations between the CPI variables (the original CPI, CALIPER-CPI, and AIQCT-derived CPIs) and overall survival in the second cohort are shown in Table 4b. The ILDB-CPI had the highest C-index among the AIQCT-derived CPIs, and it was comparable to the C-index of the CALIPER-CPI and the original CPI, similar to the observations in the first cohort. The C-index of the ILDBH-CPI was lower than that of the other CPI variables (vs. original CPI, $P=0.01$; vs. CALIPER-CPI, $P=0.01$; vs. ILD-CPI, $P=0.02$; vs. ILDB-CPI, $P=0.01$).

The Kaplan–Meier survival curves for the original CPI, the CALIPER-CPI, and the ILDB-CPI in the second cohort, generated using the cutoff values derived from the first cohort, are shown in Fig. 2D-F. There were considerable differences in overall survival between groups when any of the CPI formulas were used, similar to the findings observed in the first cohort.

Discussion

We constructed new CPI formulas based on PFT parameters to predict the volume fractions of ILD (ILD-CPI), the sum of the ILD and bronchial volume fractions (ILDB-CPI), and the sum of the ILD, bronchial, and hyperlucent volume fractions (ILDBH-CPI), which were measured with AIQCT in IPF patients. All AIQCT-derived CPIs were associated with overall survival. The C-index of the ILDB-CPI (calculated with the %FVC, %FEV_1, and %DLCO) was greater than that of the ILD-CPI (calculated with only the %FVC and %DLCO) and similar to that of the original CPI and the CALIPER-CPI in the two cohorts. The C-index of the ILDBH-CPI was lower than that of the ILD-CPI.

Table 2 Linear regression models for the associations of AIQCT variables with pulmonary function tests

		Multiple linear regression models					Linear regression models with backward selection				
AIQCT variables	**Variables**	**β**	**95% CI**		***P***	**Model R^2**	**β**	**95% CI**		***P***	**Model R^2**
ILD	Intercept	27.48	22.35	32.61	< 0.001	0.45	29.19	24.89	33.49	< 0.001	0.44
	%FVC	-0.15	-0.25	-0.05	0.005		-0.09	-0.15	-0.04	0.001	
	$\%FEV_1$	0.07	-0.04	0.18	0.23		-	-	-	-	
	%DLCO	-0.22	-0.28	-0.15	< 0.001		-0.21	-0.28	-0.15	< 0.001	
ILD and bronchi (sum)	Intercept	37.57	31.89	43.24	< 0.001	0.55	37.57	31.89	43.24	< 0.001	0.55
	%FVC	-0.25	-0.36	-0.14	< 0.001		-0.25	-0.36	-0.14	< 0.001	
	$\%FEV_1$	0.13	0.01	0.26	0.04		0.13	0.01	0.26	0.04	
	%DLCO	-0.27	-0.34	-0.21	< 0.001		-0.27	-0.34	-0.21	< 0.001	
ILD, bronchi and hyperlucencies (sum)	Intercept	39.69	31.51	47.88	< 0.001	0.41	39.48	34.81	44.15	< 0.001	0.42
	%FVC	0.01	-0.15	0.17	0.88		-	-	-	-	
	$\%FEV_1$	-0.01	-0.20	0.17	0.88		-	-	-	-	
	%DLCO	-0.42	-0.52	-0.32	< 0.001		-0.42	-0.51	-0.33	< 0.001	

The underlined coefficients and intercepts were used in formulas for AIQCT-derived CPIs. AIQCT, artificial intelligence-based quantitative computed tomographic image analysis software; %FVC, the percentage of predicted forced vital capacity; $\%FEV_1$, the percentage of predicted forced expiratory volume in one second; %DLCO, the percentage of predicted diffusing capacity for carbon monoxide; ILD, interstitial lung disease; CPI, composite physiologic index. β, regression coefficient; CI, confidence interval; R^2, coefficient of determination

Table 3 Formulas for AIQCT-derived CPIs

AIQCT-derived CPI		
ILD [ILD-CPI]	=	29.2–0.21 × %DLCO – 0.09 × %FVC
ILD and bronchi (sum) [ILDB-CPI]	=	37.6–0.27 × %DLCO – 0.25 × %FVC + 0.13 × $\%FEV_1$
ILD, bronchi and hyperlucencies (sum) [ILDBH-CPI]	=	39.5–0.42 × %DLCO
Original CPI	=	91.0–0.65 × %DLCO – 0.53 × %FVC + 0.34 × $\%FEV_1$
CALIPER-CPI	=	66.0–0.47 × %DLCO – 0.67 × %FVC + 0.32 × $\%FEV_1$

AIQCT, artificial intelligence-based quantitative computed tomographic image analysis software; CPI, composite physiological index; ILD, interstitial lung disease; %DLCO, the percentage of predicted diffusing capacity for carbon monoxide; %FVC, the percentage of predicted forced vital capacity; $\%FEV_1$, the percentage of predicted forced expiratory volume in one second; CALIPER, Computer-Aided Lung Informatics for Pathology Evaluation and Rating

Among the AIQCT-derived CPIs, the ILDB-CPI, reflecting the sum of the ILD and bronchial volume fractions, was calculated with the FVC, FEV_1, and DLCO, similar to the original CPI and the CALIPER-CPI, and had a similar accuracy to these CPIs in predicting survival. AIQCT quantifies bronchial areas separately from GGOs, reticulation and honeycombing, whereas the visual scoring method used to develop the original CPI and CALIPER do not quantify the bronchial volume fractions separately. Although a direct comparison is unavailable, a substantial proportion of the bronchial areas labeled by AIQCT may have been included in the ILD areas in the visual scoring and CALIPER evaluations, as suggested in the original articles [8, 10].

The bronchial volume fractions measured by AIQCT may reflect the severity of traction bronchiectasis. Traction bronchiectasis is associated with the severity of IPF [25] and is considered a critical component in the diagnosis of radiological usual interstitial pneumonia (UIP) patterns [26]. Previous studies have suggested that pathologically, traction bronchiectasis and honeycombing represent a continuous process [27], as honeycombing results from the collapse of fibrotic alveoli and the dilatation of terminal airways [28, 29]. Thus,

Table 4 Associations of AIQCT-derived CPIs, the original CPI and the CALIPER-derived CPI with overall survival

	a) 1st cohort (*n* = 116)				**b) 2nd cohort (*n* = 72)**			
Variables	**HR**	**95%CI**	***P***	**C-index**	**HR**	**95%CI**	***P***	**C-index**
ILD-CPI	1.22	(1.16, 1.29)	< 0.001	0.750	1.19	(1.11, 1.28)	< 0.001	0.739
ILDB-CPI	1.16	(1.12, 1.21)	< 0.001	0.759	1.14	(1.08, 1.20)	< 0.001	0.749
ILDBH-CPI	1.14	(1.10, 1.18)	< 0.001	0.729	1.11	(1.06, 1.16)	< 0.001	0.690
Original CPI	1.07	(1.05, 1.09)	< 0.001	0.765	1.06	(1.04, 1.09)	< 0.001	0.738
CALIPER-CPI	1.07	(1.05, 1.09)	< 0.001	0.749	1.06	(1.04, 1.09)	< 0.001	0.757
%FVC	0.97	(0.96, 0.99)	< 0.001	0.658	0.96	(0.94, 0.98)	< 0.001	0.710
%DLCO	0.95	(0.93, 0.96)	< 0.001	0.729	0.96	(0.94, 0.98)	< 0.001	0.690

AIQCT, artificial intelligence-based quantitative computed tomographic image analysis software; CPI, composite physiological index; ILD, interstitial lung disease; CALIPER, Computer-Aided Lung Informatics for Pathology Evaluation and Rating; ILDB, interstitial lung disease and bronchial volumes; ILDBH, interstitial lung disease, bronchial and hyperlucent volumes; %FVC, the percentage of predicted forced vital capacity; %DLCO, the percentage of predicted diffusing capacity for carbon monoxide

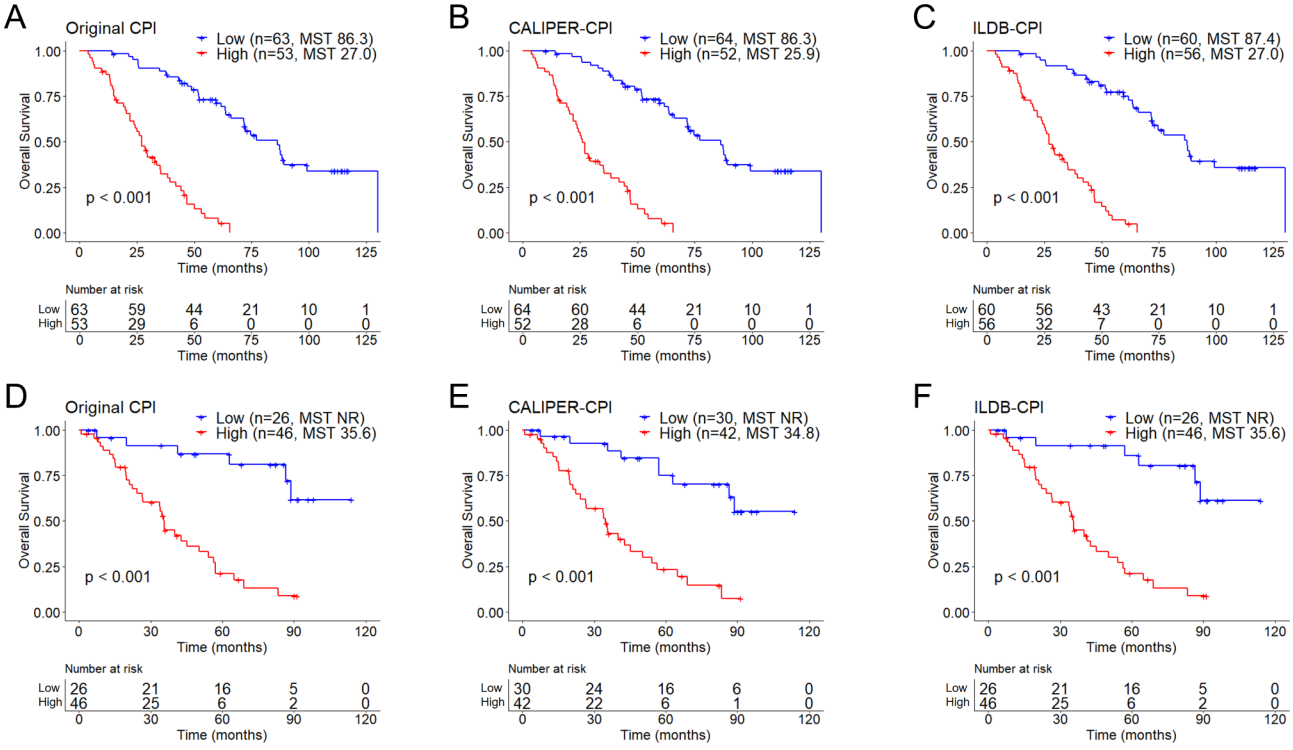

Fig. 2 Kaplan–Meier survival curves for the original CPI, the CALIPER-CPI, and the ILDB-CPI. Cutoff values were determined on the basis of time-dependent ROC curve analysis for 24-month survival in the first cohort. These cutoff values were also applied to the second cohort. (**A**-**C**) The first cohort. (**D**-**F**) The second cohort. (**A**-**F**) Low: patients with the original CPI, the CALIPER-CPI, or the ILDB-CPI lower than the cutoff value. High: patients with the original CPI, the CALIPER-CPI, or the ILDB-CPI higher than the cutoff value. (**A**) Survival curves according to the original CPI (cutoff: 46). (**B**) Survival curves according to the CALIPER-CPI (cutoff: 17). (**C**) Survival curves according to the ILDB-CPI (cutoff: 15). (**D**) Survival curves according to the original CPI (cutoff: 46). (**E**) Survival curves according to the CALIPER-CPI (cutoff: 17). (**F**) Survival curves according to the ILDB-CPI (cutoff: 15). CPI, composite physiological index; CALIPER, Computer-Aided Lung Informatics for Pathology Evaluation and Rating; ILDB, interstitial lung disease and bronchial volumes; ROC, receiver operating characteristic; MST, median survival time (months); NR, not reached

adding the bronchial volume fractions to the CPI formulas may account for the effects of traction bronchiectasis and adjacent fibrotic changes, such as microscopic honeycombing.

To interpret the inclusion of FEV_1 in the formula for ILDB-CPI, the physiological characteristics of IPF should also be considered. The ratio of FEV_1 to FVC and the ratio of forced expiratory flow at 25–75% of FVC (FEF25–75%) to FVC both increase in IPF, suggesting airway dilatation and a reduction in airway resistance [30]. Parenchymal fibrosis affects the %FVC and %DLCO more directly, whereas the $\%FEV_1$ remains relatively preserved. Although bronchial volume fractions are negatively correlated with %FVC, $\%FEV_1$, and %DLCO (Additional File: Table S1), $\%FEV_1$ corrected the overestimated associations of %FVC and %DLCO with the bronchial volume fractions in a regression model (Table 2). These findings may have led to the addition of FEV_1 to the formula for the ILDB-CPI.

In contrast, the ILDBH-CPI, which also reflects the hyperlucent volume fractions, was calculated based on %DLCO alone. Patients with fibrosis and emphysema are characterized by a relatively preserved FVC and FEV1 because the effects of restriction and traction by fibrosis and the effects of hyperinflation and expiratory airway collapse caused by emphysema presumably cancel each other out [31]. The opposing effects of fibrosis and emphysema may have caused the weaker impact of FVC and FEV1 on ILDBH-CPI and the lower coefficient of determination of ILDBH-CPI. A previous report suggested that mortality in patients with CPFE could be explained by the sum of the extents of fibrosis and emphysema [15]. In this study, the ILDBH-CPI appeared to be a weaker prognostic factor than the original CPI, the CALIPER-CPI, and the ILD-CPI. The influence of the total volume of hyperlucencies on the prognosis of IPF patients should be examined in future research.

Kaplan–Meier analysis revealed that the median survival time ranged from 24 months to 36 months in the high-risk groups according to the original CPI, the CALIPER-CPI, and the ILDB-CPI in the two cohorts. There is a consensus that lung transplantation should be considered for patients at high risk of death from lung disease within 2 years [32]. CPIs below the cutoff values indicate

a median survival time of 2–3 years; therefore, the CPI formulas may be useful in evaluating an indication for lung transplantation.

AI-based systems, such as AIQCT, are likely to be influenced by the types and volumes of training data [33]. In our preceding study, the accuracy of the AIQCT analysis was validated by confirming moderate to strong correlations between the results of AIQCT and visual scores [12]. The Dice similarity coefficients for the analysis of the similarities between the ground truth and the AIQCT images were also satisfactory. Although the AIQCT analysis is fully automatic, the results of the AIQCT analysis did not reveal any errors requiring correction in this study. However, when AI software is used, any deviation in the study subjects from the training data should always be considered. To establish AIQCT as a reliable and validated method for quantifying CT, further studies in different populations are needed.

This study has several limitations. First, the values of the PFT parameters in this study were higher than those in the original CPI study and CALIPER-CPI study, whereas the volume fractions of ILD and the hyperlucent volume fractions were lower than those in the original CPI study and CALIPER-CPI study [8, 10]. Second, antifibrotic treatment is increasingly accepted as the standard therapy for IPF, and a survival benefit has been reported in a previous meta-analysis [34]. Antifibrotic treatment after baseline may modify the disease course and thus influence the associations of CPIs at baseline with overall survival. Third, although CT examinations were conducted in the supine position at full inspiration, it is possible that the patients' effort affected the lung volumes and the volume fractions of the lung parenchymal segmentations, especially the hyperlucent volume fractions in patients with emphysema.

Conclusions

AIQCT-derived CPIs were associated with survival. The CPI reflecting the sum of the ILD and bronchial volume fractions can be used to predict the outcomes of patients with IPF with a similar performance to that of the original CPI and CALIPER-CPI. The CPI reflecting the sum of the ILD, bronchial, and hyperlucent volume fractions was not superior to the CPI reflecting the ILD volume fraction alone in predicting mortality. The effect of hyperlucent areas on functional severity and outcomes in IPF patients should be addressed in future studies.

Abbreviations

AIQCT	Artificial intelligence-based quantitative computed tomographic image analysis software
CALIPER	Computer-aided lung informatics for pathology evaluation and rating
C-index	Harrell's concordance index
CPFE	Combined pulmonary fibrosis and emphysema
CPI	Composite physiologic index
CT	Computed tomography
DLCO	Diffusing capacity for carbon monoxide
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GGO	Ground-glass opacity
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
ILDB	ILD and bronchial volumes
ILDBH	ILD, bronchial and hyperlucent volumes
IPF	Idiopathic pulmonary fibrosis
IQR	Interquartile range
PFT	Pulmonary function test
ROC	Receiver operating characteristic

Supplementary Information

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Supplementary Material 1

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Author contributions

M.U., T. Handa, K.T., K.I. and A.M. contributed to the study design. T. Handa, K.T., T.O., N.T., T.N., H.S., R.M., T.W.N., R.S., T.K., Y.N. and T. Hirai contributed to the development of computer software. M.U., R.U. and K.T. performed the data analysis. M.U. and K.T. wrote the manuscript. M.U.T. Handa, R.U., K.I., K.T., N.T., A.M., T.M., Y.S., A.Y., Y.N. and T. Hirai contributed to critical revision of the manuscript. M.U., T. Handa, S.H., Y.T., K.I., K.T., T.N., R.M., T.W.N., R.S., A.Y., K.T. and T. Hirai contributed to collection of the data. All the authors read and approved the final manuscript.

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Data availability

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Kyoto University and the Ethics Committee of Tenri Hospital approved this study (approval numbers R1353, E2119 and No. 635, respectively). The requirement for written informed consent was waived due to the retrospective design of this study. This study was conducted in accordance with the amended Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

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