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Traction Bronchiectasis/Bronchiolectasis is Associated with Interstitial Lung Abnormality Mortality

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Author Contribution

All participated in analysis and interpretation of the data. HH performed conception and design of the study. TH, MN, TH GRH, DCC, DAL, GMH, and HH created the first draft. All authors critically reviewed the manuscript and approved the final version, taking accountability for the work.

[#]:iPNet; image-based Phenotyping Network

Abstract

Purpose: To investigate if the presence and severity of traction bronchiectasis/bronchiolectasis are associated with poorer survival in subjects with ILA.

Method: The study included 3,594 subjects (378 subjects with ILA and 3,216 subjects without ILA) in AGES-Reykjavik Study. Chest CT scans of 378 subjects with ILA were evaluated for traction bronchiectasis/bronchiolectasis, defined as dilatation of bronchi/bronchioles within areas demonstrating ILA. Traction bronchiectasis/bronchiolectasis Index (TBI) was assigned as: TBI=0, ILA *without* traction bronchiectasis/bronchiolectasis: TBI=1, ILA *with* bronchiolectasis but *without* bronchiectasis or architectural distortion: TBI=2, ILA with mild to moderate traction bronchiectasis: TBI=3, ILA and severe traction bronchiectasis and/or honeycombing. Overall survival (OS) was compared among the subjects in different TBI groups and those without ILA.

Results: The median OS was 12.93 years (95%CI; 12.67 – 13.43) in the subjects without ILA; 11.95 years (10.03 – not reached) in TBI-0 group; 8.52 years (7.57 – 9.30) in TBI-1 group; 7.63 years (6.09 – 9.10) in TBI-2 group; 5.40 years (1.85 – 5.98) in TBI-3 group. The multivariable Cox models demonstrated significantly shorter OS of TBI-1, TBI-2, and TBI-3 groups compared to subjects without ILA ($P<0.0001$), whereas TBI-0 group had no significant OS difference compared to subjects without ILA, after adjusting for age, sex, and smoking status.

Conclusions: The presence and severity of traction bronchiectasis/bronchiolectasis are associated with shorter survival. The traction bronchiectasis/bronchiolectasis is an important contributor to increased mortality among subjects with ILA.

Keywords

Interstitial lung abnormality; Usual interstitial pneumonia; Pulmonary fibrosis; Traction bronchiectasis; Age Gene/Environment Susceptibility-Reykjavik Study

Introduction

Interstitial lung abnormalities (ILA) have been increasingly recognized as a common set of features on chest computed tomography (CT), occurring in 4% - 9% of smokers and 2% - 7% of nonsmokers, however, clinical evaluation and management of ILA remain to be determined [1–5]. ILA have been defined as nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis as previously reported [6, 7] in research participants without a known history of interstitial lung disease. Subjects with ILA have increased symptoms of chronic cough and shortness of breath, decreased total lung capacity, decrease diffusion capacity, reduced exercise capacity, and increased all-cause mortality [1, 2, 4, 5, 7, 8]. The progression of ILA is associated with accelerated lung function decline and an increased rate of mortality [5, 9].

Traction bronchiectasis is known as an important feature of fibrotic lung diseases, which is identified in the early stage of the disease and results in honeycomb lung in the end stage of fibrotic lung diseases. Traction bronchiolectasis is dilatation of bronchioles, which proceeds the development of traction bronchiectasis. Traction bronchiectasis/bronchiolectasis is noted

as dilatation of airway (i.e. bronchi and bronchioles) within the lung areas demonstrating ILA on CT. Pathologically, traction bronchiectasis and bronchiolectasis are thought to be the result of contraction of lung tissue surrounding airway because of fibrosis, inflammation, and scarring, which correspond to the radiologic findings of bronchiectasis and bronchiolectasis on chest CT. Several studies have reported that traction bronchiectasis was associated with mortality in patients with idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) [10, 11]. Recently, we have reported that ILA with architectural distortion, often associated with established traction bronchiectasis, has been associated with poor survival [12]. However, architectural distortion can be difficult to identify, and its reproducibility is unknown. Traction bronchiectasis and bronchiolectasis would probably represent a simpler and more reliable sign of early fibrosis in ILA.

We hypothesized that the presence and severity of traction bronchiectasis and bronchiolectasis in subjects with ILA would be associated with poorer survival. To address the hypothesis, we evaluated CT scans from 3,594 subjects in the Age Gene/Environment Susceptibility (AGES)-Reykjavik Study.

Materials and Methods

Study population

This study was approved by the institutional review boards, and all subjects provided written informed consent. The original cohort consisted of 5,764 subjects in the AGES-Reykjavik Study. The AGES-Reykjavik Study is a longitudinal birth cohort including women and men born in Reykjavik from 1907 to 1935 who are now followed by the Iceland Heart Association [13] The protocols of participant enrollment in the study have been previously reported [5, 12, 14].

The original cohort of 5,764 subjects in the AGES-Reykjavik Study have been previously studied for the presence of ILA on their chest CT scans [5, 12, 14]. ILA are defined radiologically on chest CT scans as increased lung density including nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, non-emphysematous cysts, honeycombing, and traction bronchiectasis as previously described [2, 4, 6, 7]. Of the 5,764 subjects, ILA were present in 378 (7%), were indeterminate in 1,726 (32%), and were absent in 3,216 (61%), as reported in the prior study which demonstrated that the presence of ILA was associated with higher risk of all-cause mortality [5].

The current study focused on the 378 subjects who demonstrated ILA on chest CT, to further evaluate the presence and severity of traction bronchiectasis/bronchiolectasis and to investigate the impact of traction bronchiectasis/bronchiolectasis on survival among subjects with ILA. The group of 3,216 subjects *without* ILA (and thus without traction bronchiectasis/bronchiolectasis) from the original cohort was used as a reference group in the assessment of survival. Therefore, a total of 3,594 subjects including 378 subjects with ILA and 3,216 subjects without ILA comprised the cohort of the present study.

Traction bronchiectasis on CT images and Traction Bronchiectasis/Bronchiolectasis Index (TBI)

Traction bronchiectasis/bronchiolectasis was defined as dilatation of airway (i.e. bronchi and bronchioles) within areas demonstrating ILA on chest CT. In 378 subjects with ILA, severity of traction bronchiectasis was visually evaluated by comparing the diameter of the airway with the diameter of the adjacent pulmonary artery using a categorical 5-point score: 0) none (no dilatation), 1) minimal (dilatation of *bronchioles* without obvious bronchiectasis or architectural distortion), 2) mild (dilated bronchi almost same diameters with adjacent pulmonary artery), 3) moderate (between mild and severe), and 4) severe (remarkable dilatation of bronchi including honeycombing), in the lung regions where traction bronchiectasis/bronchiolectasis was most prominent [15, 16]. Two board-certified chest radiologists (T. H. and H. H.) interpreted CT images of each subject and scored traction bronchiectasis/bronchiolectasis by consensus. The radiologists were blinded to the demographical and clinical data of the subjects.

Traction Bronchiectasis/bronchiolectasis Index (TBI) was defined from the above mentioned 5-point traction bronchiectasis score: TBI=0, when traction bronchiectasis score is 0 (ILA *without* traction bronchiectasis/bronchiolectasis): TBI=1, ILA *with* bronchiolectasis (score 1) but *without* bronchiectasis or architectural distortion (Figure 1), TBI=2, ILA with mild or moderate traction bronchiectasis (score 2 or 3) (Figure 2): TBI=3, ILA and severe traction bronchiectasis and/or honeycombing (score 4) (Figure 3).

The image analyses data were sent to Iceland Heart Association after the image review, according to the protocol. The data including survival were then provided to the investigators' team after deidentification, so that the personal data of each participant were not identifiable.

Statistical analysis

The demographics were compared among the control group and the four groups, using Steel test for age (continuous variables) and Fisher's exact test for sex and smoking history (categorical variables). Overall survival (OS) was compared among the control group and the four groups according to TBI. OS was defined as the time from the date of recruitment to the AGES-Reykjavik Study (between January 2002 and February 2006) to the date of death of any cause. Patients who were still alive by the time of analyses were censored at the last known date of follow-up. OS of the different groups were estimated using the method of Kaplan-Meier, and the log-rank test with Bonferroni correction was used to assess differences in the OS distributions between groups. The log-rank trend test was utilized to analyze trend between TBI and OS. The Cox proportional hazards models were used to estimate hazard ratios (HRs) for univariate analyses, as well as for multivariable analyses which adjusted for the three available demographic variables including age, sex, and smoking status. Statistical analyses were performed using R version 3.5.3 software (R Foundation for Statistical Computing, Vienna, Austria). All P values were two-sided and $P < 0.05$ was considered statistically significant.

Results

Table 1 provides the demographics of 3,594 subjects including 378 subjects with ILA who were subcategorized into four TBI groups (TBI-0, TBI-1, TBI-2, and TBI-3), as well as the reference group of 3,216 subjects without ILA. The subjects with ILA and traction bronchiectasis/bronchiolectasis (TBI-1, TBI-2, and TBI-3) were older (all $P < 0.001$), more likely to be male than those in the group without ILA (TBI-1 and TBI-2, $P < 0.001$; TBI-3, $P = 0.023$), whereas subjects with ILA but *without* traction bronchiectasis/bronchiolectasis (TBI-0 group) showed no significant difference in age and sex from the group without ILA ($P = 0.966$ and $P = 0.915$, respectively). The subjects with TBI-0, TBI-1, and TBI-2 were more likely to be current or former smokers compared to the group without ILA (TBI-1 and TBI-3, $P < 0.001$; TBI-2, $P = 0.006$).

Figure 4 demonstrates the Kaplan-Meier estimates of overall survival (OS) of the group without ILA (3,216 subjects) and 378 subjects with ILA categorized into four TBI groups. The median OS was 12.93 years (95% confidence interval (CI) for the median; 12.67 – 13.43 years) in the group *without* ILA; 11.95 years (95% CI; 10.03 – not reached) for the subjects in the TBI-0 group (ILA *without* traction bronchiectasis/bronchiolectasis); 8.52 years (95% CI; 7.57 – 9.30) for the subjects in TBI-1 group (ILA with *bronchiolectasis* but *without* obvious bronchiectasis or architectural distortion); 7.63 years (95% CI; 6.09 – 9.10) for the subjects in TBI-2 group (ILA with mild to moderate traction bronchiectasis); and 5.40 years (95% CI; 1.85 – 5.98) for the subjects in TBI-3 group (ILA and severe traction bronchiectasis and/or honeycombing) (Table 2). A clear trend was observed among subjects with ILA that the higher the TBI, the OS is shorter ($P = 1.2\times10^{-9}$). In the univariate Cox model, OS of TBI-1, TBI-2, and TBI-3 groups were significantly shorter compared to the reference group without ILA (TBI-1: hazard ratio (HR) = 2.178; $P < 0.0001$; TBI-2: HR = 2.647; $P < 0.0001$; TBI-3: HR = 6.847; $P < 0.0001$, each compared to the reference group without ILA). In contrast, OS of the TBI-0 group did not differ significantly from the reference group without ILA (HR = 1.136; $P = 0.375$), in spite of the fact that all subjects in the TBI-0 group did have ILA.

The multivariable Cox models also demonstrated significantly shorter OS of TBI-1, TBI-2, and TBI-3 groups compared to the reference group without ILA (TBI-1: HR = 1.628, $P < 0.0001$; TBI-2: HR = 1.744, $P < 0.0001$; TBI-3: HR = 4.328, $P < 0.0001$), whereas TBI-0 group shad no significant OS difference with the reference group without ILA (HR = 1.113, $P = 0.466$), after adjusting for age (HR = 1.13, $P < 0.0001$), sex (male vs. female; HR = 1.49, $P < 0.0001$) and smoking status (former/current vs. never smokers; HR = 1.274, $P < 0.0001$).

Further comparisons of OS among the different groups according to the ILA and TBI status were performed with the log-rank test with Bonferroni correction (Table 3). OS was significantly shorter in TBI-1, TBI-2, and TBI-3 groups compared to the subjects without ILA, whereas there was no significant difference for OS between TBI-0 group (the subject with ILA but without bronchiectasis/bronchiolectasis) and the subjects without ILA ($P = 1.00$), further confirming the results in the Cox models. Comparison of OS between TBI-0 group versus TBI-1, TBI-2, and TBI-3 groups showed that each of TBI-1, TBI-2, and TBI-3 groups has significantly shorter OS compared to TBI-0 group ($P = 0.001$, $P = 1.9\times10^{-5}$, $P =$

1.5×10^{-10}, respectively). When compared to TBI-1 group, TBI-2 group showed no significant difference for OS ($P = 1.00$), but TBI-3 group has significantly shorter OS than TBI-1. OS of TBI-3 group was also significantly shorter compared with TBI-2 group ($P = 0.0086$). The results indicate that the detailed stratification by TBI status can differentiate subgroups of subjects with different prognosis.

Discussion

To our knowledge, several studies have shown that traction bronchiectasis is associated with mortality in IPF/UIP (10, 11, 15), and in subjects with ILA (12), however, this is the first report demonstrating the association between traction bronchiectasis/bronchiolectasis and poor survival in subjects with ILA including the subjects with ILA without obvious fibrotic changes. When traction bronchiectasis index (TBI) is higher, overall survival (OS) is shorter. The subjects with TBI-1, 2, or 3 had significantly shorter OS compared to the subjects without ILA, however, in contrast, subjects with ILA but *without* traction bronchiectasis/bronchiolectasis (TBI-0) had similar OS compared to the reference group without ILA (and thus without bronchiectasis/bronchiolectasis). The results indicate that the presence of traction bronchiectasis/bronchiolectasis may be an important contributor to increased mortality among subjects with ILA, which provide important insights to further understand the clinical impact of ILA [1].

The presence of bronchiectasis among subjects with ILA is associated with older age, male sex, and current and former smoking history. The results are consistent with the prior studies that have also reported these characteristics in subjects with pulmonary fibrosis or ILA [1–5]. Miller et al from our investigational group reported that measurable increase in airway wall thickness is consistently noted in research participants with ILA and in patients with IPF, suggesting that early detectable airway abnormalities may play a role in pathophysiology of fibrotic lung diseases [17].

Traction bronchiectasis has been identified as a prognostic factor predicting poor prognosis in fibrotic lung disease patients. In 2008, Sumikawa et al investigated CT images in 98 patients with pathologically proven UIP, and reported traction bronchiectasis as a predictor of poor prognosis with HR of 1.30 (95% CI; 1.18 – 1.43) [10]. Edey and Hansell et al. independently studied CT images of 146 consecutive individuals with fibrotic idiopathic interstitial pneumonias presented between 2000 and 2004, and found traction bronchiectasis to be a powerful predictor of poor outcome (HR = 1.85; 95% CI; 1.42 – 2.40, $P < 0.001$) [16]. It has been published that the presence of traction bronchiectasis correlates with profusion of fibroblastic foci [18]. Traction bronchiectasis has been an important CT feature for probable UIP and typical UIP in the recently updated Fleischner and American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin America Thoracic Association (ALAT) criteria [19, 20]. Therefore, it is of great interest to study if the severity of traction bronchiectasis may predict OS in subjects with ILA.

Our data demonstrated that median overall survival (OS) with TBI-1 (ILA *with* bronchiolectasis but *without* bronchiectasis or architectural distortion), TBI-2 (ILA with

mild to moderate traction bronchiectasis), and TBI-3 group (ILA and severe traction bronchiectasis and/or honeycombing) were significantly shorter ($P < 0.0001$) compared to that of subjects without ILA. The subjects with TBI-1 had significantly shorter OS compared to the subjects without ILA, even though the subjects with TBI-1 had only dilation of *bronchioles* without bronchiectasis, architectural distortion or definite evidence of fibrotic lung disease yet. It is possible that bronchiolectasis is an earlier sign of fibrotic lung disease, before the development of traction bronchiectasis and architectural distortion. The subjects with TBI-0 (ILA *without* bronchiectasis/bronchiolectasis) had similar overall survival compared to the subjects in the reference group without ILA ($P = 0.375$), in spite of the fact that the subjects with TBI-0 did have ILA. There was clear trend observed that the higher the TBI, the shorter the median OS, when tested using the log-rank trend test ($P = 1.2\times10^{-9}$). The differences between every pair of TBI groups comprised of TBI-0, TBI-1, TBI-2, and TBI-3 were statistically significant except for between TBI-1 and TBI-2 as shown in Table 3, when they were analysed using the univariate log-rank test with Bonferroni correction as a supplement to further demonstrate the differences of OS among TBI groups shown in Table 2 and Figure 4 while adjusting for multiple comparisons (Kaplan-Meier survival curves). TBI remained significant in the multivariate Cox model that adjusted for other significant factors including age, sex, and smoking status, demonstrating that TBI can be an independent predictor of shorter survival in subjects with ILA. These findings indicate that TBI may play an important role in determining the clinical outcome of subjects with ILA.

Furthermore, our results demonstrated that presence of traction bronchiolectasis further stratified the subjects with ILA without obvious bronchiectasis or architectural distortion into two groups of TBI-0 and TBI-1, which have different survival (TBI-0, 11.95 years with 95% CI; 10.03 – not reached versus TBI-1, 8.52 years with 95% CI; 7.57 – 9.30; p=0.001). The result is important and unique in that it indicates the potential predictive value of identification of traction bronchiolectasis on imaging for the prognosis of subjects with ILA who do not yet demonstrate definite fibrosis such as architectural distortion or bronchiectasis. Recently, Putman et al reported ILA with definite fibrosis defined by architectural distortion was associated with a 70% increase in the risk of death in participants in the AGES-Reykjavik Study (HR=1.7, 95%CI 1.3–2.1, p<0.0001) [12]. However, this previous study did not stratify subjects with ILA *without* definite fibrosis, and thus distinct from the present study that carried out the detailed evaluation of subject with ILA without definite fibrosis with a particular focus on presence or absence of *bronchiolectasis*. We agree that is necessary to investigate if the alteration represented by TBI-1 is an early fibrosis from the histological point of view in the future.

Our study has limitations. The study population of the AGES-Reykjavik, as designed in its original protocol, includes a population of older adults. Further studies with younger population cohorts are needed. The evaluation of traction bronchiectasis was performed qualitatively by visual assessment, without using the quantitative approaches such as texture analysis, machine learning, or artificial intelligence, which is an important area of investigational focus in the future, for which the results of the current study from a large observational cohort can provide important training and validation data sets [20–25]. The traction bronchiectasis was evaluated visually by consensus of two radiologists. It has been reported that many of various CT findings in patients with fibrotic lung diseases have only

poor to good interobserver correlations. However, traction bronchiectasis had one of the highest kappa values of 0.75, when two pairs of consensus reading by two radiologists were tested in the report by Sumikawa et al. [10]. The interobserver variability was not examined in this study. It is a potential limitation that this type of approach may require those with significant experience in this area to review images. The overall survival of subjects with TBI-3 is 5.4 years, which are comparable with patients with ILD. This fact indicates that these subjects with TBI-3 probably have ILD. The analysis of survival included all-cause mortality, rather than deaths caused by ILA. It is also important to address whether and how traction bronchiectasis progresses over time and eventually lead to deaths, which will be investigated as the next step from our ongoing study of AGES-Reykjavik cohort with five-year follow-up scans.

In conclusion, among the subjects with ILA in the AGES-Reykjavik Study, the presence and severity of traction bronchiectasis/bronchiolectasis are associated with shorter survival, whereas subjects with ILA without traction bronchiectasis/bronchiolectasis had similar survival with those without ILA. Traction bronchiectasis index (TBI) may serve as a useful imaging marker for the future scheme of initial evaluation, monitoring, and management of subjects with ILA.

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Conflict of interest

MN reports personal fees from Daiichi Sankyo, personal fees from AstraZeneca, grants from Research grant to the institution from Merck, grants from Research grant to the institution from Canon Medical systems, grants from Research grant to the institution from AstraZeneca, grants from Research grant to the institution from Daiichi Sankyo, personal fees from Roche, grants from NIH, outside the submitted work; RKP reports grants from NIH, during the conduct of the study; RSJE reports grants from Boehringer Ingelheim, personal fees from Boehringer Ingelheim, personal fees from Chiesi, grants from NHBLI, outside the submitted work; and he is also a founder and co-owner of Quantitative Imaging Solutions which is a company that provides image based consulting and develops software to enable data sharing.; RSJE is also a founder and co-owner of Quantitative Imaging Solutions which is a company that provides image based consulting and develops software to enable data sharing.: Dr. Washko reports grants from NIH, grants and other from Boehringer Ingelheim, other from Quantitative Imaging Solutions, other from PulmonX, grants from BTG Interventional Medicine, grants and other from Janssen Pharmaceuticals, other from GlaxoSmithKline, other from Novartis, other from Vertex, outside the submitted work; and Dr. Washko's spouse works for Biogen.; DAL reports personal fees from Boehringer Ingelheim, personal fees from Parexel, Inc, personal fees from Veracyte, Inc, outside the submitted work; In addition, DAL has a pending patent "Systems and methods for automatic detection and quantification of pathology using dynamic feature classification.": GMH reports personal fees from Boehringer-Ingelheim, personal fees from Gerson Lehrman Group, personal fees from Mitsubishi Chemical, outside the submitted work; HH reports grants from Canon Medical System Inc, grants from Konica Minolta Inc, other from Mitsubishi Chemical Inc, other from Canon Medical System Inc, outside the submitted work.

Abbreviation

AGES-Reykjavik Study	Age Gene/Environment Susceptibility-Reykjavik Study
ILA	interstitial lung abnormality
TBI	traction bronchiectasis/bronchiolectasis index

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Highlights:

- Traction bronchiectasis (TB) is noted within interstitial lung abnormalities (ILA) on CT.
- TB is associated with shorter survival in ILA.
- ILA with dilation of bronchioles (bronchiolectasis) without TB also shows shorter survival.
- Bronchiolectasis may be an earlier sign of fibrotic lung disease including ILA.
- Traction bronchiectasis/bronchiolectasis index (TBI) predicts shorter survival in ILA.

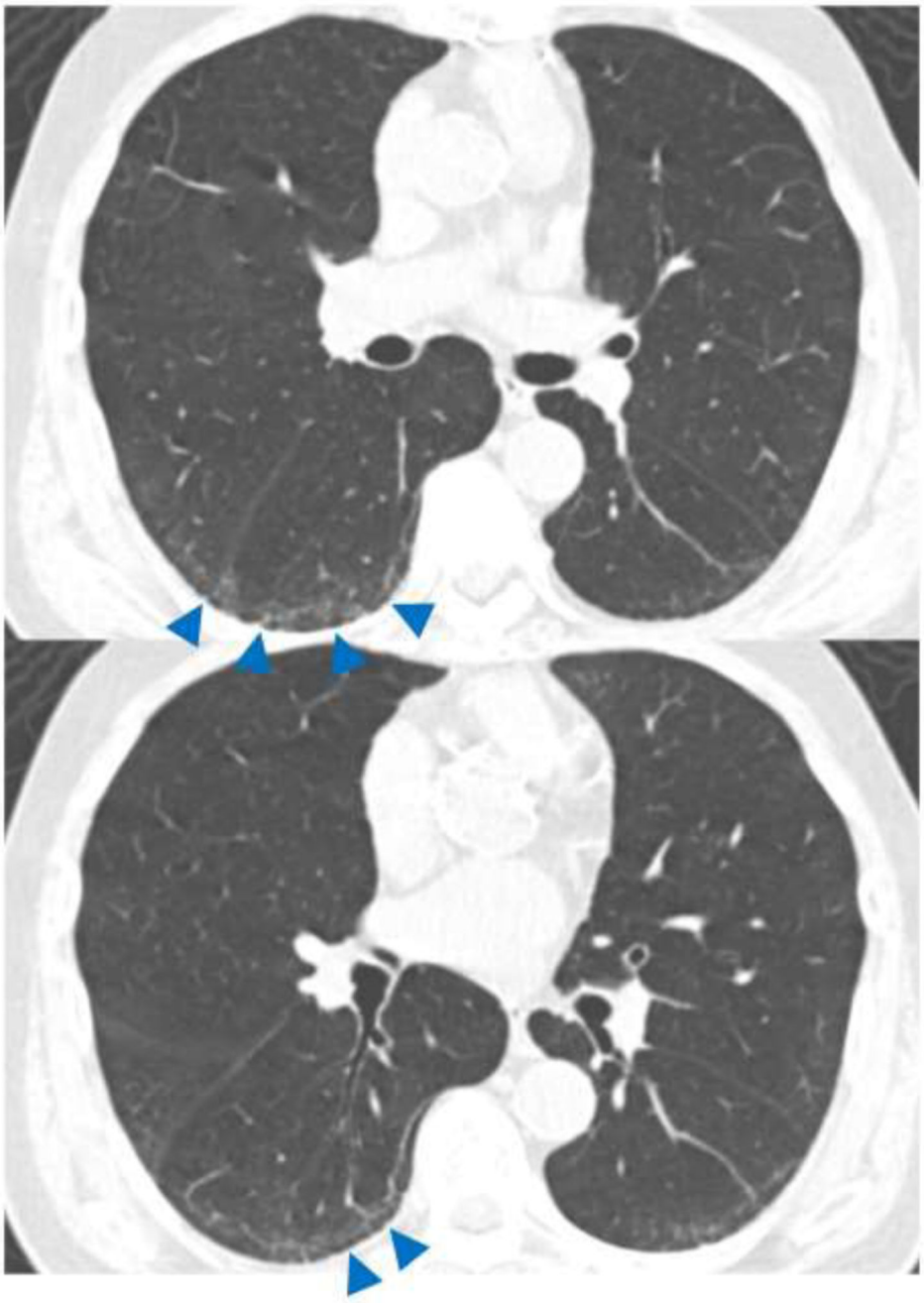


Figure 1.

TBI=1. CT images demonstrated subpleural ground-glass and reticular opacities indicating ILA. Note is made of dilatation of *bronchioles* (arrows) without obvious architectural distortion in the area of subpleural opacities of ILA. ILA, interstitial lung abnormalities; TBI, traction bronchiectasis index.

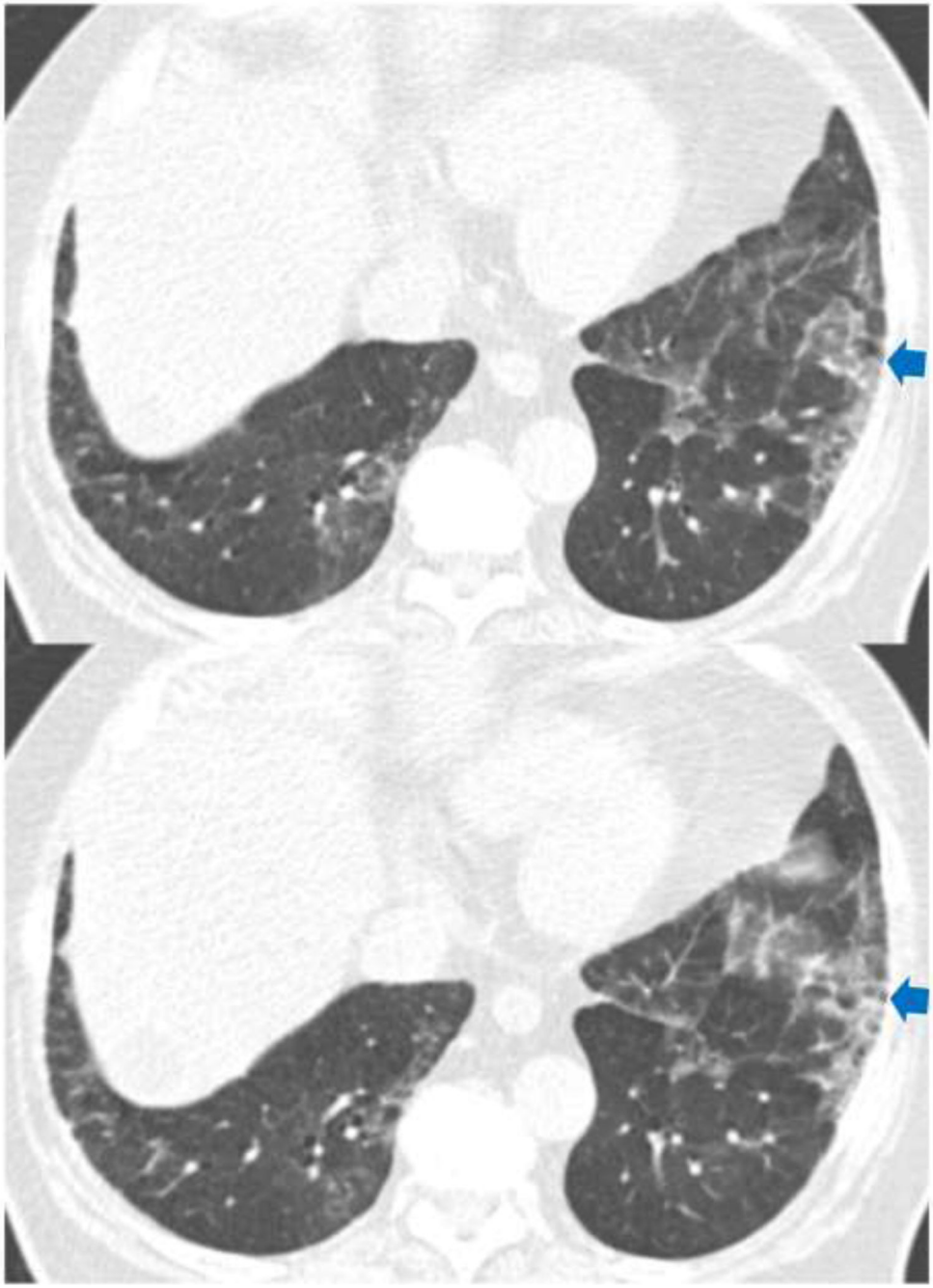


Figure 2.

TBI=2. CT images demonstrated ground-glass and reticular opacities with subpleural and basilar distribution indicating ILA. Note is made of mild bronchiectasis (arrows) associated with architectural distortion in the area of subpleural opacities of ILA. ILA, interstitial lung abnormalities; TBI, traction bronchiectasis index.

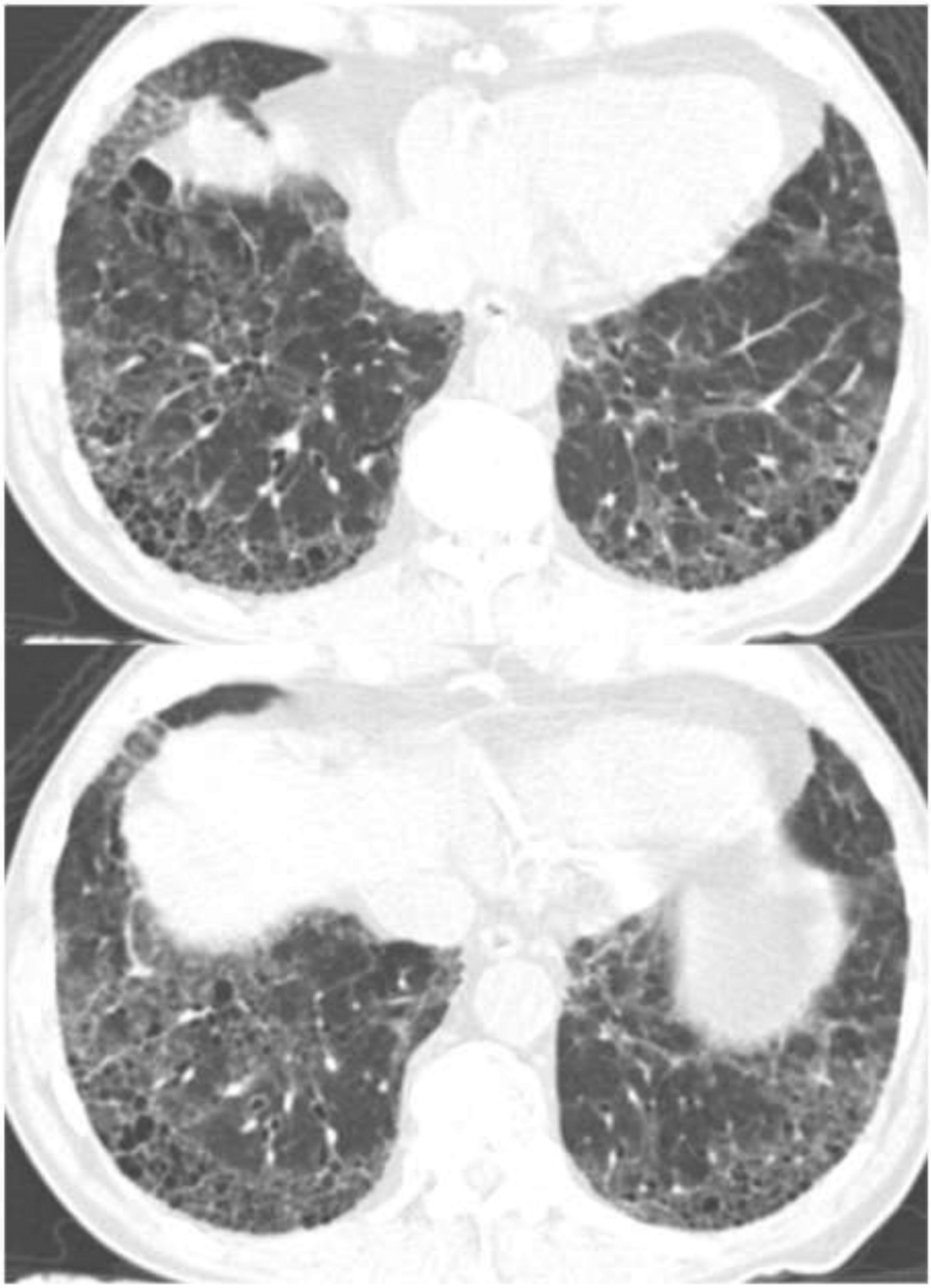
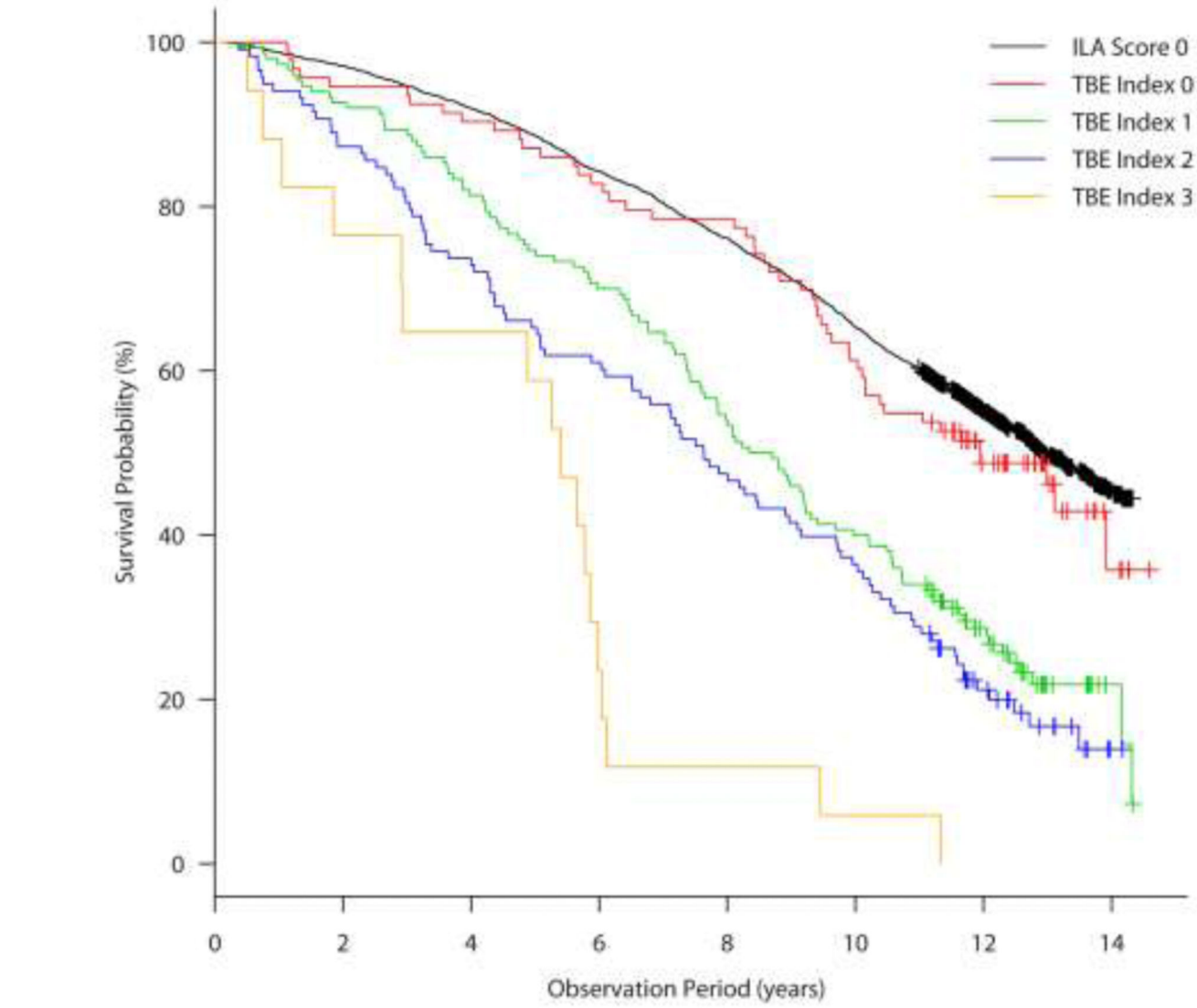


Figure 3.

TBI=3. CT images demonstrated ground-glass and reticular opacities with subpleural and basilar distribution indicating ILA. Note is made of severe bronchiectasis associated with architectural distortion as well as honeycombing. ILA, interstitial lung abnormalities; TBI, traction bronchiectasis index.



Number at risk

ILA Score 0	3216	3124	2956	2710	2449	2100	1306	175
TBE Index 0	93	88	84	77	73	57	35	5
TBE Index 1	150	139	122	105	81	60	29	3
TBE Index 2	118	103	87	72	56	43	18	1
TBE Index 3	17	13	11	4	2	1	0	0

Figure 4.

Kaplan-Meier survival curves showing percent survival provability over time in years among participants with ILA stratified by TBI = 0, 1, 2, and 3 compared with the subjects without ILA. ILA, interstitial lung abnormalities; TBI, traction bronchiectasis index.

Table 1.

Baseline characteristics of participants stratified by ILA (Interstitial lung Abnormalities) and TBI (Traction Bronchiectasis Index)

Demographics	No ILA (n=3216)	Subjects with ILA (n=378)			
		TBI-0 No TB (n=93)	TBI-1 Bronchiolectasis (n=150)	TBI-2 Mild/ moderate TB (n=118*)	TBI-3 Severe TB (n=17)
Age (years)					
Median [Range]	75 [66–96]	75 [67–94]	78 [67–92]	79 [69–91]	79 [69–92]
P value†	-	0.966	<0.0001	<0.0001	0.032
Sex					
Male	1306	37	87	70	12
Female	1910	56	63	48	5
P value†	-	0.915	<0.0001	<0.0001	0.023
Smoking History					
Never	1463	24	51	26	4
Former	1376	45	79	68	10
Current	374	22	20	24	3
Unknown	3	2	0	0	0
P value¶	-	<0.0001	0.006	<0.0001	0.087

*Include 72 subjects with mild traction bronchiectasis and 46 subjects with moderate traction bronchiectasis

†*P* value is for the comparison to the control group.

¶*P* value is for the comparison of never and former/current smokers to those in the control group.

ILA, interstitial lung abnormality; TBI, traction bronchiectasis index; TB, Traction Bronchiectasis

Table 2.

Overall Survival stratified by ILA and TBI with Univariate Cox Model using the subjects without ILA as the reference group

	Median OS (years)	**95% CI for the median OS**	**HR**	**95% CI for HR**	***P* value***
No ILA (n=3216)	12.93	12.67 – 13.43	-	-	-
TBI-0 ILA without TB (n=93)	11.95	10.03 – NR	1.136	0.857 – 1.505	0.375
TBI-1 ILA with traction bronchiolectasis (n=150)	8.52	7.57 – 9.30	2.178	1.8 – 2.635	<0.0001
TBI-2 ILA with mild/moderate TB (n=118)	7.63	6.09 – 9.10	2.647	2.153 – 3.253	<0.0001
TBI-3 ILA with sever TB/honeycombing (n=17)	5.40	1.85 – 5.98	6.847	4.237 – 11.07	<0.0001

* From univariable Cox models, in comparison with the control group

CI, confidence interval; ILA, interstitial lung abnormality; NR, not reached; TBI, traction bronchiectasis index; TB, Traction Bronchiectasis

Table 3.

Comparisons of overall survival among the subjects in subgroups stratified by ILA and TBI status, using the log-rank test with Bonferroni correction

	No ILA	TBI-0 (ILA without traction bronchiectasis/ bronchiolectasis)	TBI-1 (ILA with traction bronchiolectasis)	TBI-2 (ILA with mild/moderate traction bronchiectasis)	TBI-3 (ILA with severe traction bronchiectasis/ honeycombing)
No ILA	_	_	_	_	_
TBI-0 (ILA without traction bronchiectasis/ bronchiolectasis)	1	_	_	_	_
TBI-1 (ILA with traction bronchiolectasis)	**2.0×10^{-15}**	**0.001**	_	_	_
TBI-2 (ILA with mild/ moderate traction bronchiectasis)	**$<2.0\times10^{-16}$**	**1.9×10^{-5}**	1	_	_
TBI-3 (ILA with severe traction bronchiectasis/ honeycombing)	**$<2.0\times10^{-16}$**	**1.5×10^{-10}**	**4.6×10^{-5}**	**0.0086**	_

ILA, interstitial lung abnormality; TBI, Traction bronchiectasis index