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1 **Parenchymal destruction in asthma: Fixed airflow obstruction and lung function**

2 **trajectory**

3

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24 **A disclosure statements**

45 **Abstract (243 words / 250 words)**

46 **Background:** Fixed airflow obstruction (FAO) in asthma, particularly in non-smoking

47 subjects, is generally believed to be caused by airway remodeling. However, parenchymal

48 destruction may also contribute to FAO and longitudinal decline in forced expiratory

49 volume in 1 sec (FEV_1).

50 **Objectives**: To evaluate parenchymal destruction using emphysema indices, exponent D

51 and low attenuation area percent (LAA%) on computed tomography (CT), and test

52 whether the parenchymal destruction and airway disease are independently associated

53 with FAO and FEV_1 decline in both smoking and non-smoking asthma.

54 **Methods**: D, LAA%, wall area percent (WA%) at segmental airways, and airway fractal

55 dimension (AFD) in asthmatics were measured on inspiratory CT and compared to those

56 in chronic obstructive pulmonary disease (COPD) patients.

57 **Results**: D was lower and LAA% was higher in COPD (N = 42) and asthma with FAO

58 (N = 101) than in asthma without FAO (N = 88). The decreased D and increased LAA%

59 were associated with FAO regardless of smoking status or asthma severity. In

60 multivariable analysis, decreased D and increased LAA% were associated with an

61 increased odds ratio of FAO and decreased FEV_1, irrespective of WA% and AFD.

62 Moreover, decreased D affected the longitudinal decline in FEV_1 in severe asthmatics,

63 independent of smoking status .

64 **Conclusions**: Asthmatics with FAO showed the parenchymal destruction regardless of

65 smoking status and asthma severity. The parenchymal destruction was associated with an

66 accelerated FEV_1 decline, suggesting the involvements of both airway and parenchyma

67 in the pathophysiology of a subgroup of asthma.

68

69 **Clinical implications (27/30 words)**

70 Decreased D, together with increased LAA% on CT, reflecting parenchymal destruction,

71 was associated with fixed airflow obstruction and accelerated FEV_1 decline in asthmatics

72 irrespective of smoking status.

73 **Capsule summary (33/35 words)**

74 The contribution of parenchymal damages to pulmonary function impairments was

75 independent of airway diseases, severity of asthma, smoking status, and blood eosinophil

76 counts. This distinct feature broadens our insight into the pathophysiology of asthma.

77 **Keywords**

78 Asthma, computed tomography, fractal, low attenuation area, non-smokers, parenchyma

79 **Abbreviations**

80 AFD : airway fractal dimension, AQLQ : Asthma Quality of Life Questionnaire, ATS :

81 American Thoracic Society, BSA : body surface area, CT : computed tomography,

82 COPD : chronic obstructive pulmonary disease, D_{Lco} : carbon monoxide diffusing

83 capacity, FAO : fixed airflow obstruction, FeNO : fractional exhaled nitric oxide, FEV_1 :

84 forced expiratory volume in 1 sec, FVC :   forced vital capacity, HU : Hounsfield Unit,

85 ICS : inhaled corticosteroids, Kco : transfer coefficient, LABA : long acting β2 agonist,

86 LAC : low attenuation cluster, LAA% : low attenuation area percent, LA : airway luminal

87 area, OCS : oral corticosteroids, RB1 : right apical bronchus, RB8 : lateral basal bronchus,

88 WA : airway wall area, V_A : alveolar volume, WA% : wall area percent

89

INTRODUCTION

Asthma has a complex pathophysiology with diverse disease history and therapeutic responses [1]. Despite advances in clinical management and treatment, such as inhaled corticosteroids (ICS), bronchodilators, and biologics, a subgroup of patients with asthma still develops fixed airflow obstruction (FAO) and shows an accelerated decline in lung function [2-4]. Therefore, uncovering its underlying mechanisms is urgently needed.

Airway disease is believed to be a main pathology of asthma that is characterized by wall remodeling and lumen narrowing [5, 6], and the involvement of small airway disease has been increasingly recognized, particularly in severe asthma [7]. Moreover, cigarette smoking evokes airway inflammation and potentiates structural airway changes [8, 9]. Meanwhile, autopsy studies have shown the destruction of alveolar walls attached to small airways, termed alveolar attachments [10], and centrilobular emphysema [11] in non-smoking asthmatics. A recent study by Tonga *et al.* [12] demonstrated the loss of elastic recoil in older longstanding non-smoking asthmatics with FAO, even after recommended treatments. However, whether parenchymal destruction has distinct functional roles, irrespective of airway remodeling, has not been elucidated.

Computed tomography (CT) enables comprehensive assessments of parenchyma and airways. The relative contribution of airways and emphysema to airflow limitation on CT has been studied in chronic obstructive pulmonary disease (COPD) [13], but less so in asthma, especially in non-smokers. CT studies have shown a decrease in lung density [14] and an increase in low attenuation area percentage (LAA%) in asthma [15], which is generally used as an emphysema index. Nonetheless, LAA% alone cannot fully address the question about whether emphysematous destruction was present, because simple local lung expansion without alveolar destruction would also increase LAA% on

114   CT.

115   Fractals can be used for morphological lung analysis. An object exhibiting self-

116   similarity at various length scales possesses a fractal property, which is governed by a

117   power law characterized by the exponent D. Mishima *et al.* discovered that the

118   cumulative frequency of size distribution of low attenuation clusters on CT follows a

119   power law characterized by the exponent D in COPD, and suggested in a spring network

120   simulation that a decrease in D reflects alveolar wall destruction causing coalescence of

121   neighboring airspaces [16]. Yuan *et al*. confirmed a close association between D on CT

122   and emphysema on histology and suggested that D might enable sensitively detecting

123   parenchyma destruction [17]. This concept was further confirmed by Tanabe *et al.* who

124   showed in a computer simulation that when LAA% increases, a decrease in exponent D

125   could reflect coalescence of low attenuation clusters representing emphysematous

126   destruction rather than simple local lung expansion [18]. Meanwhile, Mitsunobu *et al.*

127   showed a reduction in exponent D in severe asthma [15], whereas Gupta *et al.* showed

128   no difference in the exponent D between severe asthmatics, mild to moderate asthmatics,

129   and controls [19].

130   It was hypothesized that in addition to airway disease, parenchymal destruction

131   occurs in a subgroup of asthmatics regardless of smoking status and that both the airway

132   disease and parenchymal destruction could be involved in FAO and accelerated lung

133   function decline in a subgroup of asthmatics. To test this hypothesis, we evaluated

134   parenchymal destruction using a combination of exponent D and LAA% in asthmatics

135   and COPD patients. Then we explored the relative contributions of the exponent D,

136   LAA%, and CT airway disease indices to an increased risk of FAO and lower forced

137   expiratory volume in 1 sec (FEV_1) at the baseline, and greater longitudinal decline in

138   FEV$_1$ in the prospective asthma cohort including smokers.

139   **METHODS**

140   This study was approved by the Ethics Committee of the Hokkaido University School of

141   Medicine (approval number, 02-001) and registered in the University Hospital Medical

142   Information Network Clinical Trials Registry (UMIN-CTR) system

143   (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno = R000003917; ID no.

144   000003254). All subjects provided written informed consent, and 213 subjects (127 with

145   severe and 86 with non-severe asthma) were eligible for the initial study [20]. All

146   participants stayed at the Hokkaido University Hospital for 2 days of initial screening

147   (baseline visit), and patients with severe asthma were followed up yearly on an outpatient

148   basis for 5 years. Detailed information is described in the online supplement.

149   **Asthma patients**

150   Subjects were participants of the Hokkaido-based Investigative Cohort Analysis for

151   Refractory Asthma (Hi-CARAT). Those with CT data suitable for further assessment at

152   baseline entered this study. We classified the subjects into two groups based on the

153   number of cigarette packs they smoked (non-smokers (<10 pack-years) and smokers (≥10

154   pack-years). Subjects with severe asthma were categorized based on the American

155   Thoracic Society (ATS) criteria of refractory asthma in 2000, with slight modifications

156   of the inhaled corticosteroid doses due to the availability in Japan [20]. Hi-CARAT study

157   participants were scheduled to undergo four times pre-bronchodilator and post-

158   bronchodilator spirometry at inhalation of 400 μg of salbutamol and 400 μg of

159   oxytropium on the first day, followed by 400 μg of salbutamol on the second day at the

160   baseline examinations. We adopted FEV_1/forced vital capacity (FEV_1/FVC) when the

161   best FEV_1 was obtained among the four spirometry (two pairs of pre- and post-

162   bronchodilator spirometry) during the baseline examinations. Then we defined patients

163   with $FEV_1/FVC < 0.7$ as asthmatics with FAO.

164   **COPD Patients**

165   For morphological and physiological comparisons with asthma patients, we included mild

166   to moderate COPD patients whose post-bronchodilator FEV_1 (% of predicted) was 50%

167   or more to match spirometric impairment to that of asthmatics. We selected patients who

168   completed the exams of the fifth-year visit of the Hokkaido COPD cohort [21, 22], which

169   was the nearest visit to the baseline exams of this asthma cohort. COPD patients

170   underwent CT examinations and pulmonary function tests under the same conditions as

171   asthmatic patients did.

172   **Pulmonary function tests**

173   Pulmonary function tests met the requirements of the Japanese Respiratory Society

174   Guidelines [23]. Carbon monoxide diffusing capacity (D_{Lco}) and transfer coefficient

175   (D_{Lco}/V_A, Kco), based on the single breath method, were measured in all patients

176   according to these guidelines.

177   **Quantitative chest CT**

178   Asthma and COPD patients underwent chest full-inspiration CT in the supine position

179   using a multidetector row spiral CT scan with a 64-detector array (Aquilion Multi, TSX-

180   101A/6A; Toshiba Medical Systems, Tochigi, Japan) and pulmonary function tests on the

181   same day at the Hokkaido University Hospital. The acquisition parameters were 120 kVp,

182   300 mA, 64 detectors, 0.5 mm collimation, slice thickness of 0.5 mm, 0.5 s/rotation,

183   helical pitch of 41, and smooth and sharp reconstruction kernels (FC03 and FC52).

184   Parenchymal analysis was conducted using FC03, while airway analysis was done using

185   FC52.

186   **Assessment of D, LAA%, WA%, and AFD**

187   LAA% was calculated as the volume percentages of low attenuation voxels < -950 and

188   < -910 Hounsfield Unit (HU) (LAA%950 and LAA%910, respectively) [24].

189   Additionally, neighbouring voxels < -910 HU were three-dimensionally identified as a

190   low attenuation cluster (LAC), and the volume of each LAC was obtained. The log-

191   transformed volume of the LACs and the log-transformed cumulative count of LACs

192   larger than the given volume were plotted on the x and y-axis, respectively. The absolute

193   slope of the linear regression line was measured as the exponent D [25]. A lower D

194   indicates greater extent of parenchymal destruction.

195   To quantify airway structure, the airway tree was three-dimensionally segmented, and

196   airway fractal dimension (AFD) was calculated based on the box-counting method as

197   reported [15, 26, 27], Moreover, airway luminal area (LA), airway wall area (WA), wall

198   area percent (a ratio of wall area to summed area from wall and lumen (WA%)) at the

199   right apical (RB1) and lateral basal (RB8) segmental airways were measured, and

200   averaged LA and WA were normalized by body surface area (BSA).

201   **Statistical analyses**

202   For group comparisons of asthma with and without FAO in non-smokers and smokers,

203   and in non-severe and severe asthmatics, Student-T test or Wilcoxon signed rank test

204   were used. For comparisons among asthma with and without FAO, and COPD, ANOVA

205   followed by Tukey's multiple comparison test, Dunn test for continuous variables, and

206   chi-square test for categorical variables were used. Spearman's correlation analysis was

207   performed to examine the relationships between D, LAA%910, and %FEV$_1$. Longitudinal

208   FEV$_1$ changes were calculated using values from the first-year visit (one year after the

209   screening examination including CT) to the sixth-year visit. Patients with more than 3

210   FEV$_1$ values were eligible (N = 102). We excluded pulmonary function test values at the

211   screening examination, as they were disproportionately higher compared to those

212   obtained in following years. (Online supplementary Table E1).

213   Multivariable logistic regression analysis was used to test the association between D or

214   LAA%910 and FAO, and multivariable linear regression analyses were used to examine

215   the association between D or LAA%910 and %FEV$_1$ after adjustment for sex, asthma

216   severity and atopic status, as a categorical variable and age, body mass index (BMI), pack-

217   years, blood eosinophil counts, AFD and WA% for as a continuous variable. Further

218   multivariable linear regression models were used to examine associations between D or

219   LAA%910 and the longitudinal FEV$_1$ changes, after adjustment for the abovementioned

220   factors excluding asthma severity.

221

222   **RESULTS**

223   Of 189 eligible asthma patients, 101 were categorized as having FAO and were compared

224   with COPD patients (Online supplementary Figure E1).

225

226   **Comparisons between asthma with and without FAO and COPD**

227   Clinical, physiological, and CT imaging characteristics are shown in Table 1.

228   Asthmatics without FAO were more predominantly female compared to asthmatics with

229   FAO and COPD patients. Duration of asthma was longer in asthmatics with FAO than

230   those without FAO. Although the severity of asthma and CT measured lung volume

231   (adjusted by predicted TLC value) did not differ between asthmatics with and without

232   FAO, %FEV$_1$ and FEV$_1$/FVC were lower and %RV and RV/TLC were higher in

233   asthmatics with FAO. Moreover, LA/BSA and AFD were lower, WA% and LAA%950

234   were higher in asthmatics with FAO. To increase the sensitivity to detect mild

235   parenchymal destruction, LAA%910 was also measured. In Figure 1, larger clusters of

236   low attenuation area < −910 HU were found in asthmatics with FAO (the exponent D =

237   0.84) compared to those without FAO (the exponent D = 1.35), as visualized by

238   different regression line slopes. Figure 2 further shows that D decreased and LAA%910

239   increased in asthmatics with FAO and COPD patients compared to asthmatics without

240   FAO. In contrast, D and LAA%910 did not differ between severe and non-severe

241   asthmatics.

242   **Associations of D and LAA%910 with FAO in asthmatics depending on severity and**

243   **smoking status**

244   LAA%910 was higher in smokers with asthma than in non-smokers with asthma (p=0.01),

245   while D showed no significant difference between -smokers with asthma and non-

246   smokers with asthma (p=0.09). Since smoking could affect airway and parenchyma

247   structure, comparisons of physiological and CT indices between asthmatics with and

248   without FAO were performed in non-smokers and smokers, separately. Table 2 and Figure

249   3 show that D decreased, LAA%950 and LAA%910 increased in asthmatics with FAO

250   compared with in asthmatics without FAO both in non-smokers and smokers while no

251   difference in CT derived lung volume adjusted by predicted TLC value was found.

252   Furthermore, in subgroup analysis of severe or non-severe asthmatics (Supplementary

253   Table E2), decreased D and increased LAA%910 were found in non-severe and severe

254   asthmatics with FAO (Figure 4). Meanwhile, D and LAA%910 showed no differences

255   between severe asthma and non-severe asthma both in non-smokers and smokers. (Online

256   supplementary Figure E2)

257

258   **Associations of D and LAA%910 with FAO, %FEV$_1$ at baseline, and longitudinal**

259 **FEV$_1$ decline**

260 Multivariable analyses were performed to explore whether the parenchymal destruction

261 estimated using LAA%910 and exponent D and airway disease estimated using WA%

262 and AFD on CT were associated with FAO (Table E3) and FEV$_1$ independent of

263 demographics, and pack-years (Table 3). Due to a close association between D and

264 LAA%910, these were separately included in models. Decreased D and AFD as well as

265 increased LAA%910 and WA% were independently associated with FAO and %FEV$_1$

266 after adjustment for age, sex, BMI, pack-years, asthma severity, atopy, and blood

267 eosinophil count.

268 Furthermore, Table 4 shows that D, but not LAA%910, was significantly associated with

269 FEV$_1$ decline (-33.8±23.4 ml/year, (mean±SD)) after adjustment for age, sex, BMI, pack-

270 years, atopy, and blood eosinophil count in severe asthma patients (N = 102). Online

271 supplementary Figure E3 shows no significant correlations between D and blood

272 eosinophil count or the percentage of eosinophils or neutrophils in sputum. (rho = -0.04,

273 p = 0.54, rho =- 0.08, p = 0.31, rho = -0.02, p = 0.75, respectively)

274

275

276 **DISCUSSION**

277 This study showed that D was lower and LAA%910 was higher in asthmatics with FAO

278 than in those without FAO regardless of smoking status. It further revealed that the

279 parenchymal destruction estimated from decreased D and increased LAA%910 as well as

280 the airway diseases estimated from decreased AFD and increased WA% were

281 independently associated with a higher odds ratio of FAO and a lower %FEV$_1$ after

282 adjusting for severity of asthma, smoking history, and other potentially confounding

283 factors. Moreover, a decrease in D at the baseline was associated with a greater

284 longitudinal FEV_1 decline in a five-year observation of severe asthma. These data suggest

285 that the parenchymal destruction occurs in asthmatics with FAO, and the parenchymal

286 destruction and airway disease may independently affect trajectory of lung function in

287 both smokers and non-smokers with asthma.

288   Airway remodeling is a well-established asthma feature [28], and parenchyma in

289 asthma was believed to remain intact. However, this concept is inconsistent with several

290 reports on parenchymal disorders in never smokers with moderate to severe asthma,

291 including the destruction of alveolar attachments [10], presence of centrilobular

292 emphysema [11], and loss of elastic recoil [12]. In this context, the found associations of

293 decreased D with FAO, lower FEV_1, and an accelerated FEV_1 decline (regardless of

294 smoking status and airway diseases) substantially increase the understanding of the

295 functional role of parenchyma in patients with asthma, which could be extended to that

296 in patients with Asthma – COPD overlap in the future.

297   One could argue that LAA% increases due to local lung expansion without   the

298 parenchymal destruction. However, we deem this unlikely, since an increase in

299 LAA%910 and LAA%950 was accompanied by a decrease in D in non-smoking and

300 smoking asthmatics with FAO, and because the combinational change in LAA% and D

301 in asthmatics was comparable to that in COPD. Furthermore, the finding that CT derived

302 lung volume adjusted by predicted TLC in asthmatics with and without FAO did not differ

303 ($92.4 \pm 17.0\%$ and $88.1 \pm 17.4\%$) suggests that a decrease in D cannot be explained solely

304 by lung expansion. Alternatively, a reduction in D can be explained by a previous work

305 by Mishima *et al.* who showed that a rupture of alveolar walls and coalescence of

306 damaged areas would be required for a decrease in D [16]. Further, Tanabe *et al.* showed

307 that when LAA% increased, a decrease in D was induced by coalescence of neighboring

308 pre-existing low-density CT regions, and not by simple enlargement of pre-existing low-

309 density regions presumably reflecting local lung expansion [18]. Therefore, the observed

310 combinational change in LAA% and D in asthmatics with FAO could be at least partially

311 reflective of alveolar airspace enlargement due to alveolar wall destruction besides local

312 lung expansion.

313 Notably, the parenchymal destruction assessed as the combination of increased

314 LAA% and decreased D was found in both smoking and non-smoking asthmatics with

315 FAO. Moreover, the CT finding of the parenchymal destruction was accompanied by a

316 decrease in Kco in smoking asthmatics with FAO, suggesting that the parenchymal

317 destruction in smoking asthmatics with FAO could be consistent with emphysematous

318 destruction observed in smoking-related COPD as previously reported [29]. In contrast,

319 a decrease in K_{CO} was not found in non-smoking asthmatics with FAO. We postulate that

320 morphological changes and functional impairments induced by the parenchymal

321 destruction in non-smoking asthmatics with FAO may not be exactly the same as those

322 in smoking asthmatics with FAO.

323 Decreased D was associated with a longitudinal FEV_1 decline, irrespective of

324 airway disease and established factors leading to it, including smoking habits [30] and

325 blood eosinophil count [31, 32]. This finding has augmented the significance of the

326 parenchymal destruction in asthma. There are few reports that CT metrics of airways and

327 parenchyma possibly serve as predictive markers of lung function decline or

328 exacerbations [33]. The present data showed no significant correlations between D and

329 blood eosinophil count or eosinophil% and neutrophil% in sputum, despite treatment with

330 anti-inflammatory agents such as inhaled (ICS) and oral corticosteroid (OCS) under

331 adequate adherence. This finding is concordant with a previous study by Tonga *et al.* [12]

332 showing that no changes were observed in eosinophil or neutrophil counts and

333 inflammatory cytokines in bronchoalveolar lavage of non-smoking older asthmatics with

334 FAO after 2 months of ICS/long acting β2 agonist (LABA) treatment. Collectively, these

335 findings suggest that a one-fits-all anti-inflammatory drug strategy does not improve the

336 trajectory of pulmonary function in asthmatics who are characterized by both the airway

337 disease and parenchymal destruction.

338 Moreover, in autopsy studies, Maud. *et al.* [10] showed an increase in abnormal

339 alveolar attachments and a decrease in elastic fiber content in small airways and peri-

340 bronchial alveoli in fetal asthma with no clinical evidence of emphysema, whereas Gelb

341 *et al.* showed diffuse mild centrilobular emphysema in non-smokers with asthma [11]. In

342 COPD, inflammation of small airway disease, imbalance of proteases and anti-proteases,

343 oxidative stress [34], and exaggerated mechanical force [35, 36] could drive emphysema

344 development. We speculate that protease activity and mechanical force on alveolar walls

345 might be enhanced in a subgroup of asthmatics who eventually develop disrupted normal

346 tissue integrity and FAO. This phenomenon may be partly concordant with the evidence

347 that a bronchoconstriction without inflammation causes airway remodeling [37].

348 No significant difference in D between severe and non-severe asthmatics was

349 found in this study. This is consistent with a study by Gupta *et al.* [19], but not with a

350 study by Mitsunobu *et al.*, who showed a significant reduction in exponent D in non-

351 smokers with severe asthma compared to those with mild to moderate asthma (please see

352 further discussion in the online supplement) [15].

353 This study defined low attenuation regions using CT values of −910HU and −950

354 HU as cut-offs to calculate LAA% and of −910HU as cut-off to calculate the exponent D.

355   Moreover, this study also used fractals to evaluate airway structure using AFD [25, 26].

356   Few papers have performed combinational analysis using the two power law indicators

357   [27], D and AFD. These topics are further discussed in the online supplemental discussion.

358   The current study has several limitations. First, only CT data at baseline are

359   available. Consecutive CT data would confirm the results and broaden the perspectives

360   for the clinical significance and proper utilization of exponent D as a CT-based biomarker.

361   Second, annual FEV_1 decline was calculated from one year after baseline examination,

362   while the CT scan was performed at baseline. Participants with severe asthma had been

363   prescheduled to undergo baseline examinations during a two-day hospital stay, but to

364   undergo follow-up examinations by visiting the hospital as out-patient . Consequently,

365   the results of spirometry at the baseline examination were disproportionally better than

366   those at the follow-up examinations in many patients, possibly due to adequate rest, less

367   allergen burden, or less stimuli causing the worsening of asthma control. Therefore, we

368   did not include the baseline data to calculate the longitudinal change in FEV_1 in the

369   present analyses. Nonetheless, we believe that the FEV1 decline data should be accurate

370   because it was calculated using serial data obtained annually from year 1 to year 5 visits.

371   Third, the longitudinal analysis on FEV_1 was performed in severe asthma patients, so

372   future studies should determine the effect of parenchymal destruction on FEV_1 in patients

373   across different severities.

374   In conclusion, parenchymal evaluation with a combination of LAA% and D on

375   CT showed that the parenchymal destruction occurs in asthmatics with persistent airflow

376   limitation regardless of smoking status and asthma severity. Moreover, decreased D and

377   increased LAA% were associated with airflow limitation, and decreased D affected the

378   longitudinal FEV_1 decline independent of WA% and AFD in asthma. Of note, no

379   association between D and inflammatory markers was found. Therefore, more attention

380   should be paid to the possibility that both airway disease and parenchymal destruction

381   underlie physiological impairments and may affect clinical outcomes in a subgroup of

382   asthma, who requires personalized managements and novel interventions in the future.

383

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509

510

511 **FIGURE LEGENDS**

512

513 **Figure 1. The representative asthmatics with or without fixed airflow obstruction.**

514 Coronal images (A) and three-dimensional imaging (B) on CT of asthmatics with FAO

515 and without FAO. Larger clusters of low attenuation area < −910 HU were found in

516 asthmatics with FAO (the exponent D = 0.84, regression line in red (C)) compared to

517 those without FAO (the exponent D = 1.35, regression line in blue (C)).

518

519 **Figure 2. Comparisons of D, LAA%910 in asthma with or without fixed airflow**

520 **obstruction, and COPD and in non-severe and severe asthmatics**

521 (A) Exponent D was the lowest, and LAA%910 was the highest in COPD, followed by

522 asthma with fixed airflow obstruction (FAO), asthma without FAO. (B) There were no

523 significant differences in exponent D and LAA%910 between non-severe and severe

524 asthmatics.

525

526 **Figure 3. Comparisons of D, LAA%910 between asthmatics with or without fixed**

527 **airflow obstruction in non-smokers and smokers.**

528 D decreased and LAA%910 increased in cases of fixed airflow obstruction both in non-

529 smokers and smokers.

530

531 **Figure 4. Comparisons of D, LAA%910 between non-severe and severe asthmatics**

532 **with or without fixed airflow obstruction.**

533 D decreased and LAA%910 increased in cases of fixed airflow obstruction both in non-

534 severe and severe asthmatics.

535 **TABLES**

536 **Table 1.** Characteristics of subjects with asthma with or without fixed airflow obstruction

537 and those with COPD

	Asthma without FAO	Asthma with FAO	COPD
Patients, N	88	101	42
Male, N (%)	25 (28.4)	50 (49.5)	36 (85.7) §
Age, years	55.9 ± 14.6*†	65.2 ± 9.9	69.3 ± 7.6
BMI, kg/m^2	25.6 ± 5.8†	24.5 ± 4.2†	22.6 ± 3.4
Severe, N (%)	54 (61.4)	72 (71.3)	
Smokers, N (%)	25 (28.4)	45 (44.6)	42 (100) §
Pack-years	10.4 (0–11.5)†	16.1 (0–26.8)†	60.0 (40.8-68.9)
Duration of asthma, years	14.5 ± 12.7*	25.1 ± 15.5	
Atopy, N (%)	62 (70.5)	64 (63.4)	
AQLQ	5.6 (5.0–6.4)	5.7 (5.0–6.4)	
Daily ICS dose, mg	1235.2 ± 628.9	1371.0 ± 765.5	
Maintenance OCS use, N (%)	16 (18.2)	30 (29.7)	
Eo,µL	289.4 ± 0.46*	350.8 ± 0.45†	175.7± 0.31
IgE, IU/ml	414.1 ± 0.68	414.8 ± 0.60	
FeNO, ppb	37.4 (0.35)	39.6 (0.32)	
%FEV$_1$, %	117.5 ± 19.7*†	97.6 ± 21.0 †	81.2 ± 19.9
FEV$_1$/FVC, %	78.7 ± 5.6*†	58.1 ± 7.7	60.3 ± 11.6
%RV, %	105.2 ± 18.6*†	116.9 ± 22.3†	130.9 ± 28.3
RV/TLC, %	33.8 ± 6.1*†	38.7 ± 6.6	38.6 ± 7.8
%TLC, %	110.5 ± 12.9	114.3 ± 14.1	111.1 ± 16.8
% D$_{Lco}$, %	99.4 ± 20.9†	107.3 ± 22.8 †	81.6 ± 23.1
%Kco, %	110.1 ± 18.8†	107.1 ± 25.0 †	70.4 ± 19.5
%CT-LV, %	88.1 ± 17.4	92.4 ± 17.0	89.6 ± 15.3
LA/BSA, mm^2/m^2	14.7 ± 7.5*†	11.6 ± 6.2	11.4 ± 5.8
WA%, %	56.6 ± 6.7*†	61.0 ± 6.5	60.2 ± 5.8
WA/BSA, mm^2/m^2	18.1 ± 5.8	17.0 ± 6.1	16.2 ± 5.6
AFD	1.95 ± 0.05*	1.92 ± 0.05	1.93 ± 0.04
Exponent D	1.08 (0.07)*†	1.02 (0.06)†	0.97 (0.08)
LAA%910, %	10.0 (0.59)*†	19.8 (0.40)†	29.1 (0.36)
LAA%950, %	0.47 (0.58)*†	2.65 (0.68)†	9.37 (0.68)

538 Data are shown as the mean ± standard deviation, median (interquartile range),

539 geometric mean (log10 SD), or number (%).

540   *; $p < 0.05$, compared with asthma with FAO.

541   †; $p < 0.05$, compared with COPD.

542   §; $p<0.05$, between asthma without FAO, asthma with FAO and COPD.

543   FAO : fixed airflow obstruction, BMI : body mass index, AQLQ : Asthma Quality of

544   Life Questionnaire, ICS : inhaled corticosteroids, OCS : oral corticosteroids, Eos : blood

545   eosinophil count, FeNO : fractional exhaled nitric oxide, FEV_1 : forced expiratory

546   volume in 1 sec, RV : residual volume, TLC : total lung capacity, D_{Lco} : diffusing

547   capacity for carbon monoxide, Kco : carbon monoxide transfer coefficient, %CT-LV :

548   CT-derived lung volume adjusted by predicted value of total lung capacity, LA : airway

549   luminal area, WA : airway wall area, BSA : body surface area, AFD : airway fractal

550   dimension, LAA : low attenuation area.

551   **Table 2.** Comparisons between asthmatics with or without fixed airflow obstruction in

552   non-smokers and smokers

	Non-smokers		Smokers	
	Without FAO	With FAO	Without FAO	With FAO
Patients, N	63	56	25	45
Male, N (%)	12 (19.1)	13 (23.2)	13 (52.0) *	37(82.2)
Age, years	56.1 ± 15.5*	65.1 ± 10.3	55.4 ± 12.4*	65.4 ± 9.4
BMI, kg/m^2	25.1 ± 4.9	24.7 ± 4.7	26.8 ± 7.6	24.2 ± 3.6
Severe, N (%)	40 (63.5)	34 (60.7)	14 (56.0) *	38 (84.4)
Pack-years	1.7 (0-3.8)	1.1 (0−1.1)	32.2 (11.7-41.5)	34.9 (16.1−46)
Duration of asthma, years	14.0 ± 12.5*	27.8 ± 15.2	14.9 ± 13.5*	21.7 ± 15.4
AQLQ	5.6 (5.0-6.4)	5.8 (5.4-6.4)	5.6 (5.0-6.5)	5.5 (4.8-6.5)
%FEV$_1$, %	120.3 ± 22.5*	104.3 ± 21.8	116.4 ± 18.6*	92.2 ± 18.9
FEV$_1$/FVC, %	79.1 ± 5.7*	58.9 ± 6.7	77.7 ± 5.4*	57.1 ± 8.8
%RV, %	103.2 ± 17.7*	114.1 ± 21.1	110.4 ± 20.1	120.4 ± 23.4
RV/TLC, %	33.5 ± 6.3*	39.1 ± 6.4	34.5 ± 5.8*	38.2 ± 6.9
%TLC, %	110.8 ± 12.8	113.8 ± 13.9	109.6 ± 13.2	114.5 ± 14.6
% D$_{Lco}$, %	100.3 ± 19.8	107.3 ± 21.0	97.3 ± 23.7	107.4 ± 25.2
%Kco,%	112.7 ± 19.5	117.1 ± 22.0	103.7 ± 15.5	94.7 ± 22.9
%CT-LV, %	87.0 ± 17.9	93.2 ± 16.0	90.6 ± 16.1	91.3 ± 18.4
LA/BSA, mm^2/m^2	14.1 ± 6.5*	10.5 ± 5.7	16.2 ± 9.6	13.1 ± 6.5
WA%, %	56.7 ± 7.2*	61.8 ± 6.9	56.4 ± 5.2*	60.0 ± 5.8
WA/BSA, mm^2/m^2	17.3 ± 4.5*	15.9 ± 5.2	20.0 ± 8.0	18.4 ± 6.9
AFD	1.95 ± 0.05*	1.91 ± 0.06	1.95 ± 0.05	1.93 ± 0.04
LAA%910, %	9.36 (0.62)*	17.6 (0.43)	11.8 (0.50)*	22.5 (0.35)
LAA%950, %	0.29 (0.54)*	1.56 (0.66)±	0.91 (0.67)*	4.00 (0.66)

553   Data are shown as the mean ± standard deviation, median (interquartile range),

554   geometric mean (log$_{10}$ SD), or number (%).

555   *: P < 0.05, compared with asthmatics with FAO

556   FAO : fixed airflow obstruction, BMI : body mass index, AQLQ : Asthma Quality of

557   Life Questionnaire, FEV$_1$: forced expiratory volume in 1 sec, FVC :   forced vital

558   capacity,   RV : residual volume, TLC : total lung capacity, D_{Lco} : diffusing capacity

559   for carbon monoxide, Kco : carbon monoxide transfer coefficient, %CT-LV : CT-

560   derived lung volume adjusted by predicted value of total lung capacity. LA : airway

561   luminal area, WA : airway wall area, BSA : body surface area, AFD : airway fractal

562   dimension, LAA : low attenuation area.

563 **Table 3.** Multivariable analysis to explore factors associated with FEV$_1$ in asthma at the

564 baseline evaluation

	Model 1			Model 2		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
D	9.48	5.47-13.5	<0.0001			
LAA%910				-5.75	-11.0 - -0.52	0.03
WA%	-0.39	-0.77- -0.01	0.046	-0.55	-0.94 - -0.16	0.006
AFD	10.8	5.78 -15.8	<0.0001	11.5	6.32 - 16.8	<0.0001
Age	-0.01	-0.24 - 0.22	0.91	-0.18	-0.40 - 0.05	0.12
Female	-8.43	-11.4 - -5.50	<0.0001	-9.48	-12.6- -6.31	<0.0001
BMI	-0.32	-0.87 - 0.23	0.25	-0.03	-0.59 - 0.52	0.90
Pack-years	-0.01	-0.24 - 0.03	0.14	-0.13	-0.28 - 0.01	0.07
Severe asthma	-5.12	-8.03 - -2.22	0.0006	-5.78	-8.81 - -2.75	<0.0001
Atopy	0.53	-2.21 - 3.28	0.70	0.80	-2.08 - 3.67	0.55
Eo	-6.03	-11.5 - -0.59	0.03	-7.25	-12.9- -1.59	0.01

565 Odds, Chi-squared test and estimated values were calculated for 0.1 increase in D and

566 AFD, for 1 increase in other continuous variables.

567 LAA : low attenuation area, WA : wall area, AFD : airway fractal dimension, BMI : body

568 mass index, Eo : blood eosinophil count,

569 Eo and LAA%910 were log10 transformed.

570

571

572   **Table 4.** Multivariable analysis to explore baseline factors associated with subsequent

573   longitudinal decline in FEV_1 in asthma

	Model 1			Model 2		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
D	8.89	1.48 - 16.3	0.02			
LAA%910				-9.34	-19.2 - 0.56	0.06
WA%	0.13	-0.68 - 0.94	0.75	-0.07	-0.86 - 0.72	0.86
AFD	-1.74	-11.4 - 7.86	0.72	-0.28	-9.90 - 9.33	0.95
Age	-0.03	-0.49 - 0.43	0.91	-0.15	-0.61 - 0.31	0.51
Female	2.34	-3.54 - 8.22	0.43	0.79	-5.30 - 6.88	0.79
BMI	-0.04	-1.12 - 1.03	0.94	0.18	-0.88 - 1.23	0.74
Pack-years	0.09	-0.18 - 0.36	0.51	0.03	-0.24 - 0.30	0.82
Atopy	-3.54	- 8.92 -1.83	0.19	-2.19	-7.60 - 3.22	0.42
Eo	4.14	-5.67 - 13.9	0.40	3.12	-6.70 - 12.9	0.53

574   Estimated values were calculated for 0.1 increase in D and AFD, for 1 increase in other

575   continuous variables.

576   LAA : low attenuation area, WA :wall area, AFD : airway fractal dimension. BMI : body

577   mass index, Eo : blood eosinophil count

578   Eo and LAA%910 were log10 transformed.

1   **Online repository**

2 **Parenchymal destruction in asthma : Fixed airflow obstruction and lung function**

3 **trajectory**

4

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26   **Contents**

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33

34 **1. Supplemental Methods**

35 In the Hokkaido-based investigative cohort analysis for refractory asthma (Hi-CARAT),

36 patients with severe asthma were recruited from Hokkaido University Hospital and 29

37 affiliated hospitals and clinics between February 2010 and September 2012 [E1].

38 Respiratory physicians diagnosed asthma according to the Global Initiative on Asthma

39 criteria [E2]. The definition of severe asthma was based on the American Thoracic

40 Society criteria of refractory asthma in 2000 [E1], requiring one or two major and two

41 minor criteria.

42 **Major criteria**

43 In order to achieve asthma control ,

44 1. Treatment with continuous or near continuous (>50% of year) oral corticosteroids

45 2. Requirement for treatment with high-dose inhaled corticosteroids:

46 We modified the inhaled corticosteroid doses due to differences in their availability in

47 Japan as follows:

48 Flutide®≥800 μg, Pulmicort®≥1200 μg, QVAR®≥600 μg, Alvesco®≥600 μg,

49 Asmanex® ≥600 μg, Adoair® ≥1000 μg, Symbicort® ≥960 μg

50 **Minor criteria**

51 1. Requirement for daily treatment with a controller medication in addition to inhaled

52 corticosteroids, e.g., long-acting β-agonist, theophylline, or leukotriene antagonist

53 2. Asthma symptoms requiring short-acting β-agonist use on a daily or near daily basis

54 3. Persistent airway obstruction (FEV_1<80% predicted; diurnal PEF variability>20%)

55 4. One or more urgent care visits for asthma per year

56 5. Three or more oral steroid "bursts" per year

57   6. Prompt deterioration with <25% reduction in oral or inhaled corticosteroid dose

58   7. Near-fatal asthma event in the past. Additionally, we also recruited mild to moderate

59   asthma in stable condition for at least 6 months, without high doses of inhaled or oral

60   corticosteroids.

61   **Asthma patients**

62   Subjects were participants of Hi-CARAT. The subjects whose   CT data were available

63   at baseline were included and classified into non-smokers (<10 pack-years) and smokers

64   (≥10 pack-years). Following the protocol of the Hi CARAT study, the subjects

65   underwent four times of baseline spirometry such as pre-bronchodilator and post-

66   bronchodilator (400 μg of salbutamol) examinations on the first day and pre-

67   bronchodilator and post-bronchodilator (400 μg of oxytropium followed by 400 μg of

68   salbutamol) examinations on the second day. According to the previous papers of the

69   Hi-CARAT study, we had applied the best FEV_1 among the four spirometries to the

70   present analysis. We defined the forced expiratory volume in 1 s/forced vital capacity

71   (FEV_1/FVC) ratio < 0.7 when the best FEV_1, was obtained, as fixed airflow obstruction

72   (FAO).

73   Participants stayed at Hokkaido University Hospital for 2 days for initial screening,

74   which corresponds to the baseline visit (year 0), and were consecutively followed up

75   yearly on an outpatient basis (Visit 1-6) for 5 years as outpatients. Participants

76   underwent pulmonary function tests and CT on the same day.

77

78   **Statistical analyses**

79   Student-T test or Wilcoxon signed rank test were used for multiple comparisons of

80   asthma with and without FAO in non-smokers and smokers, and in non-severe and

81   severe asthmatics. Parametric and nonparametric continuous variables were compared

82   between asthma with and without FAO, and COPD using ANOVA followed by Tukey's

83   multiple comparison test, and   Wilcoxson signed rank test followed by Dunn's

84   multiple comparison test, respectively. Chi-square test were used for categorical

85   variables. Spearman's correlation analysis was used to investigate the associations

86   between exponent D, low attenuation area (LAA) %910, and %FEV$_1$. Longitudinal

87   changes in FEV$_1$ were calculated using data from the first-year visit (one year after the

88   screening examination including CT) to the sixth-year visit. Patients whose FEV$_1$ was

89   measured   more than 3 times were included to calculate the FEV1 change (N = 102).

90   Values from pulmonary function test at the screening examination were excluded

91   because the data obtained at the screening were disproportionately higher than those

92   obtained in following years. (please see Online supplementary table E1).

93   Moreover, association between exponent D or LAA%910 and FAO was examined using

94   multivariable logistic regression models, and   association between exponent D or

95   LAA%910 and %FEV$_1$ was also tested using multivariable linear regression models

96   adjusted for categorical variables including sex, asthma severity and atopic status, and

97   continuous variables of age, body mass index (BMI), pack-years, blood eosinophil counts,

98   AFD and WA%. Additionally, associations between exponent D or LAA%910 and the

99   longitudinal FEV$_1$ changes were tested using multivariable linear regression models

100 adjusted for the abovementioned factors other than asthma severity.

101

6

2. Supplemental Results

Of 189 eligible asthma patients, 101 were categorized as having FAO and were compared with COPD patients (Online supplementary Figure E1).

Associations of D and LAA%910 with FAO in asthmatics depending on severity and smoking status

Since smoking could affect airway and parenchyma structure, comparisons of physiological and CT indices between asthmatics with and without FAO were performed in non-smokers and smokers, separately. Table 2 and Figure 3 show that D decreased, LAA%950 and LAA%910 increased in asthma with FAO compared with in asthma without FAO both in non-smokers and smokers while no difference in CT derived lung volume adjusted by predicted TLC value was found. Furthermore, in subgroup analysis of severe or non-severe asthmatics (Supplementary Table E2), decreased D and increased LAA%910 were found in non-severe and severe asthmatics with FAO (Figure 4). Meanwhile, D and LAA%910 showed no differences between severe asthma and non-severe asthma both in non-smokers and smokers. (Online supplementary Figure E2)

Associations of D and LAA%910 with FAO, %FEV$_1$ at baseline, and longitudinal FEV$_1$ decline

Multivariable analyses were performed to explore whether the parenchymal destruction estimated using LAA% and exponent D and airway disease estimated using WA% and AFD on CT were associated with FAO (Table E3) and FEV$_1$ independent of demographics, and smoking history (Table 3). Due to a close association between D and LAA%910, these were separately included in models. Decreased D and AFD as well as

125   increased LAA%910 and WA% were independently associated with FAO and %FEV$_1$

126   after adjustment for age, sex, BMI, pack-years, asthma severity, atopy, and blood

127   eosinophil count.

128   Furthermore, Table 4 shows that D, but not LAA%910, was significantly associated

129   with FEV$_1$ decline (-33.8±23.4 ml/year, (mean±SD)) after adjustment for age, sex, BMI,

130   pack-years, atopy, and blood eosinophil count in severe asthma patients (N = 102).

131   Online supplementary Figure E3 shows no significant correlations between D and blood

132   eosinophil count or the percentage of eosinophils or neutrophils in sputum. (rho=-0.04,

133   p=0.54, rho=-0.08, p=0.31, rho=-0.02, p=0.75, respectively)

134

3. Supplemental Discussion

No significant difference in D between severe and non-severe asthmatics was found in this study. This is consistent with a study by Gupta *et al.* [E3], but not with a study by Mitsunobu *et al.*, who showed a significant reduction in exponent D in non-smokers with severe asthma compared to those with mild to moderate asthma [E4] . While Mitunobu *et al.* defined the exponent D using two-dimensional low attenuation clusters, the present study and Gupta *et al.* used three-dimensional low attenuation clusters. Moreover, this difference presumably arises from the differences in severity of airflow between the studies. In this study, D decreased when FAO occurred in non-severe and severe asthma. Therefore, parenchymal destruction could have physiological effects and induce FAO regardless of asthma severity.

This study defined low attenuation regions using CT values of −910HU and −950 HU as cut-offs to calculate LAA% and of -910HU as cut-off to calculate the exponent D. Because the number of low attenuation clusters was too small to calculate the regression line slope on the log-log plot (the exponent D), especially in asthmatics with almost normal CT findings when using −950HU as the cut-off, we decided to use the −910 HU cut-off to take more clusters of low attenuation for the rigorous calculation of the exponent D (D). Since previous reports [E5] used a −910HU cut-off to detect mild emphysema and that the extent of lung density reduction is generally milder in asthmatics than COPD, we believe that LAA%910 and D are valid to detect subtle parenchymal disorders in asthmatics.

This study also used fractals to evaluate airway structure using AFD [E6]. Few papers have performed combinational analysis using the two power law indicators [E7],

158   D and AFD. The finding that lower AFD and D were independently associated

159   with %FEV_1 in asthma suggests that airflow limitation is determined by the

160   parenchymal destruction and airway structure in asthmatics. Considering that airflow

161   limitation in COPD is affected by emphysema and airway disease, further comparisons

162   of airflow limitation determinants between COPD and asthma should be performed in

163   future studies.

4. References

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11

187   **5. Supplemental Figure Legends**

188

189   **Figure E1. Flowchart of the participants with asthma and chronic obstructive**

190   **pulmonary disease.**

191   Patients with asthma who participated in the initial study were enrolled. One severe

192   asthma patient was excluded because of the missing post-bronchodilator spirometry

193   data on the same day as CT exam. Patients with non-severe asthma, 18 patients without

194   CT data required for parenchymal and airway indices, and 5 patients examined using a

195   different CT scanner were excluded. Patients with COPD, of whom %FEV1 was 50%

196   or more were included.

197   COPD, chronic obstructive lung disease; CT, computed tomography; FEV_1, forced

198   expiratory volume in 1 sec

199

200   **Figure E2. Comparisons of D, LAA%910 between non-severe and severe**

201   **asthmatics in non-smokers and smokers.**

202   D did not differ between non-severe and severe asthmatics in non-smokers and smokers.

203

204   **Figure E3. Relationships between D and blood eosinophil counts, eosinophil%, and**

205   **neutrophil% in sputum.**

206   No significant correlations were found between D and blood eosinophil counts,

207   eosinophil%, and neutrophil% in sputum. (rho = -0.04, p = 0.54, rho = -0.08, p = 0.31,

208   rho = -0.02, p = 0.75, respectively)

209

210   **6. Supplemental Tables**

211

212   **Table E1. %FEV$_1$ at baseline and follow-up visits**

	baseline	First year	Second year	Third year	Fourth year	Fifth year	Sixth year
%FEV$_1$, %	102.7±20.6	88.1±19.0	87.6±20.4	86.5±19.4	81.9±27.3	85.5±21.0	85.4±21.4

213   Data are shown as the mean ± standard deviation.

214   FEV$_1$, forced expiratory volume in 1 sec.

215   **Table E2.** Comparisons between patients with or without fixed airflow obstruction in

216   severe and non-severe asthmatics.

	Non-severe asthma		Severe asthma	
	Without FAO	**With FAO**	**Without FAO**	**With FAO**
Patients, N	34	29	54	72
Male, N (%)	13 (38.2)	12 (41.4)	12 (22.2)	38 (52.8)
Age, years	63.4 ± 12.3*	70.8 ± 7.8	51.2 ± 14.0*	63.0 ± 9.7
BMI, kg/m^2	24.1 ± 4.4	23.4 ± 3.0	26.6 ± 6.4	24.9 ± 4.6
Smokers, N (%)	11 (32.4)	7 (24.1)	14 (25.9) *	38 (52.8)
Pack-years	13.4 (0-17.9)	7.1 (0-8.3)	8.5 (0-10.6)*	19.8 (0-31.1)
Duration of asthma, years	15.6 ± 12.5*	27.1 ± 17.5	14.0 ± 13.0*	24.3 ± 14.7
AQLQ	6.1 (5.8-6.7)	6.2 (5.8-6.6)	5.3 (4.8-6.1)	5.4 ()
%FEV$_1$, %	124.5 ±21.4*	104.6 ± 23.8	113.1 ±17.5*	94.8 ± 19.3
FEV$_1$/FVC, %	77.3 ± 4.5*	59.3 ±7.5 20.6	79.6 ± 6.1*	57.6 ± 7.8
%RV, %	100.5 ± 16.5*	109.5 ± 20.6	108.2 ± 19.4*	119.9 ± 22.4
RV/TLC, %	34.1 ± 5.9*	37.8 ± 6.0	33.6 ± 6.3*	39.0 ± 6.9
%TLC, %	111.0 ± 10.5	115.9 ± 13.1	110.1 ± 14.2	113.4 ± 14.5
%DL$_{co}$, %	106.2 ± 22.6	116.4 ± 27.2	95.1 ± 18.8*	103.7 ± 19.9
%Kco ,%	107.6 ± 18.0	111.9 ± 17.6	111.7 ± 19.3	105.1 ± 27.2
%CT-LV, %	90.0 ± 15.5	94.1 ± 17.5	86.8 ± 18.5	91.7 ± 16.9
LA/BSA, mm^2/m^2	14.6 ±5.8*	11.2 ± 6.7	14.8 ± 8.5*	11.8 ±6.0
WA%, %	56.1 ±7.5*	61.9 ± 6.7	57.0 ± 6.1*	60.7 ± 6.4
WA/BSA, mm^2/m^2	17.7 ± 3.9	16.7 ± 6.1	18.3 ± 6.8	17.1 ± 6.1
AFD	1.95 ± 0.05	1.94 ± 0.05	1.95 ± 0.06	1.91 ± 0.05
LAA%910, %	12.2(0.59)*	20.1(0.31)	8.7(0.58)*	19.7(0.43)
LAA%950, %	0.77(0.66)*	1.78(0.51)	0.27(0.52)*	3.009(0.74)

217   Data are shown as the mean ± standard deviation (SD), median (interquartile range),

218   geometric mean (log10 SD), or number (%). *: P < 0.05, compared with asthmatics with

219   FAO. FAO : fixed airflow obstruction, BMI : body mass index, AQLQ : Asthma

220   Quality of Life Questionnaire, FEV$_1$: forced expiratory volume in 1 sec, FVC :   forced

221   vital capacity,   RV : residual volume, TLC : total lung capacity, DL$_{co}$: diffusing

222   capacity for carbon monoxide, Kco : carbon monoxide transfer coefficient, %CT-LV :

223   CT-derived lung volume adjusted by predicted value of total lung capacity. LA : airway

224   luminal area, WA : airway wall area; BSA : body surface area, AFD : airway fractal

225   dimension, LAA : low attenuation area.

226 **Table E3.** Multivariable analysis to explore factors associated with fixed airflow

227 obstruction in asthma at the baseline examination

	Model 1			Model 2		
	Odds (95%CI)	Chi-squared test	p-value	Odds(95%CI)	Chi-squared test	p-value
D	0.20 (0.08 - 0.43)	19.8	<0.0001			
LAA%910				11.4 (3.74–35.0)	25.8	<0.0001
WA%	1.11 (1.04 - 1.18)	10.2	0.001	1.12 (1.05–1.19)	14.0	0.0002
AFD	0.28 (0.12 - 0.61)	10.1	0.002	0.26 (0.11–0.59)	10.8	0.001
Age	1.06 (1.02 - 1.11)	8.98	0.003	1.10 (1.05–1.15)	23.3	<0.0001
Female	0.15 (0.06 - 0.42)	15.4	<0.0001	0.36 (0.13–0.97)	4.26	0.04
BMI	1.53 (0.92 - 1.09)	0.01	0.92	0.99 (0.90–1.08)	0.10	0.76
Pack-years	0.58 (0.06 - 5.65)	0.22	0.64	0.99 (0.97–1.02)	0.20	0.65
Severe asthma	2.66 (1.05 - 6.72)	4.41	0.04	4.25 (1.60–11.3)	9.26	0.002
Atopy	0.88 (0.37 - 2.13)	0.07	0.78	0.79 (0.31–1.99)	0.25	0.62
Eo	1.42 (0.61 - 3.47)	0.65	0.42	1.56 (0.65–3.74)	1.01	0.31

228 Odds, Chi-squared test and estimated values were calculated for 0.1 increase in D and

229 AFD, for 1 increase in other continuous variables.

230 LAA : low attenuation area, WA : wall area, AFD : airway fractal dimension. BMI : body

231 mass index, Eo : blood eosinophil count

232 Eo and LAA%910 were log10 transformed.

233

Parenchymal destruction in asthma: Fixed airflow obstruction and lung function trajectory

Bronchial Asthma

Airway remodeling: smaller inner luminal area, higher wall area percent on CT
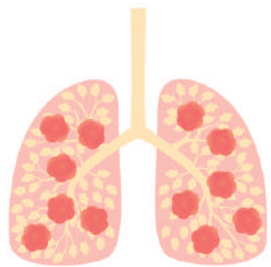
Parenchymal destruction: larger low attenuation clusters on CT

$FEV_1\%$ predicted

non-FAO (n=88)

FAO (n=101)
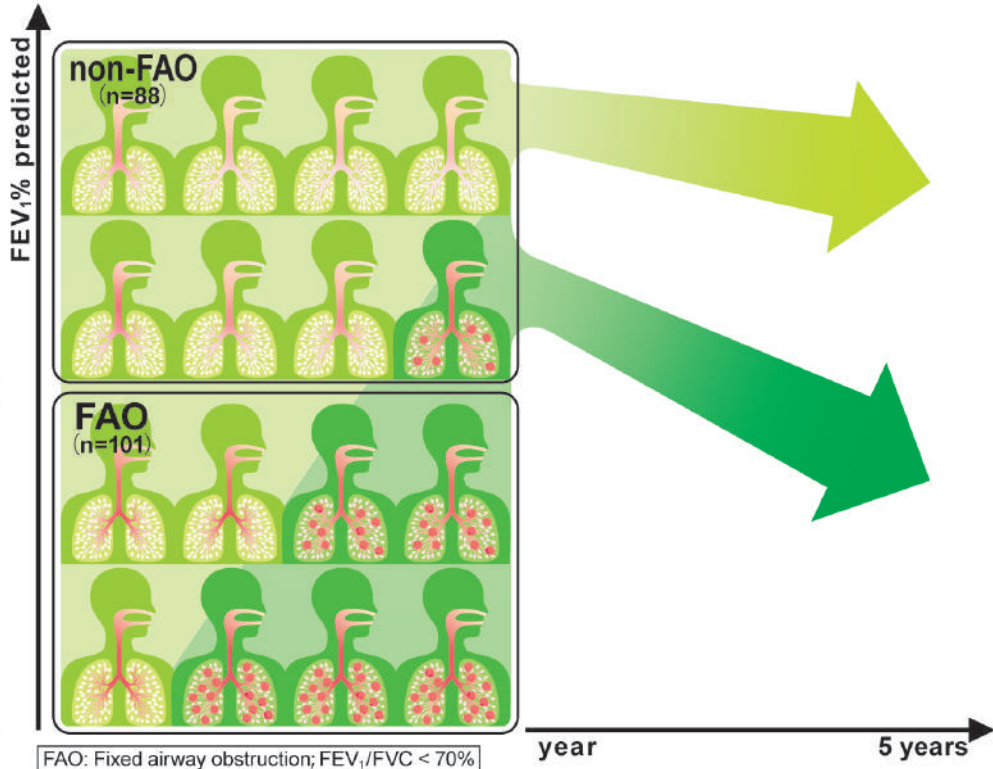
FAO: Fixed airway obstruction; $FEV_1/FVC < 70\%$

year
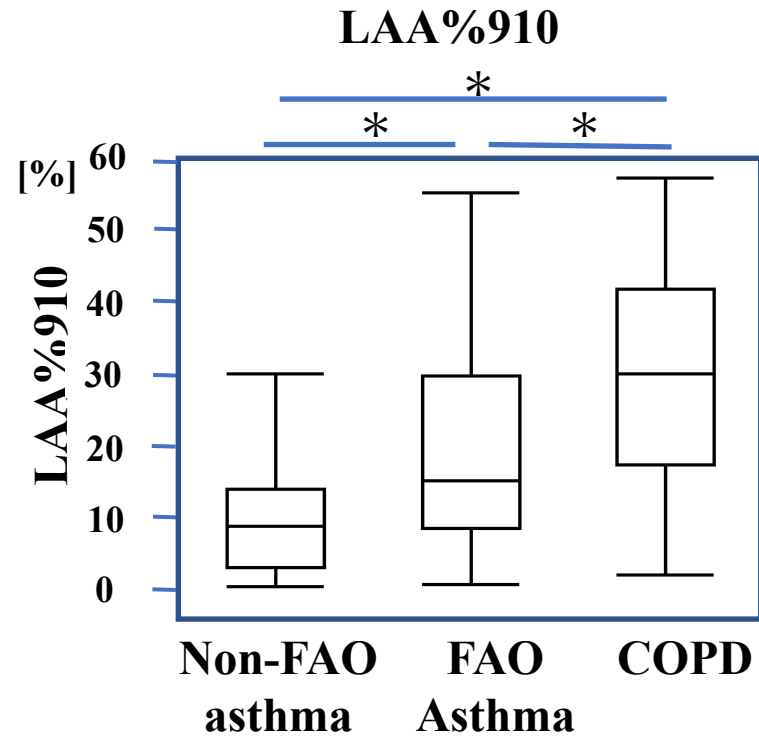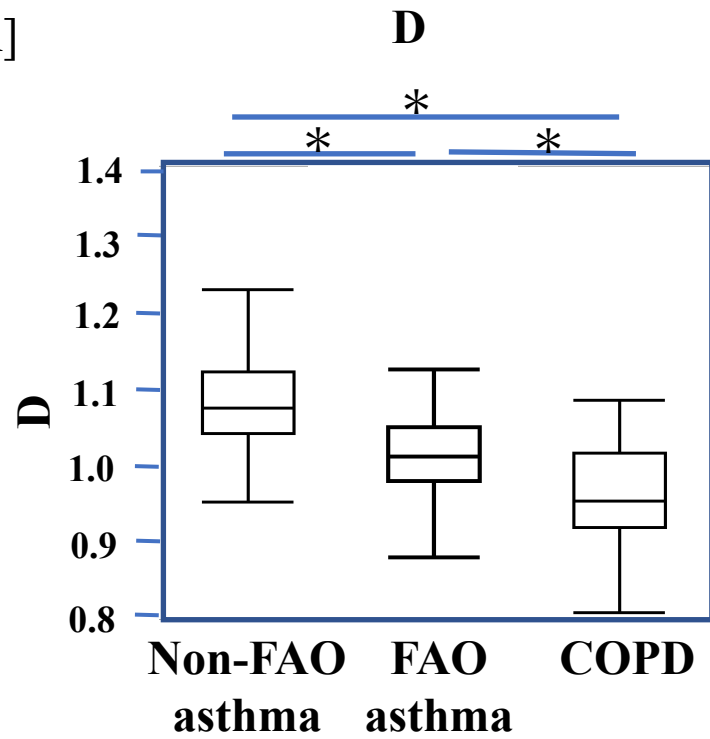
5 years

Figure 1.

[A] Asthma with FAO   Asthma without FAO

[B]

[C] Cumulative distribution function vs. Cluster sizes
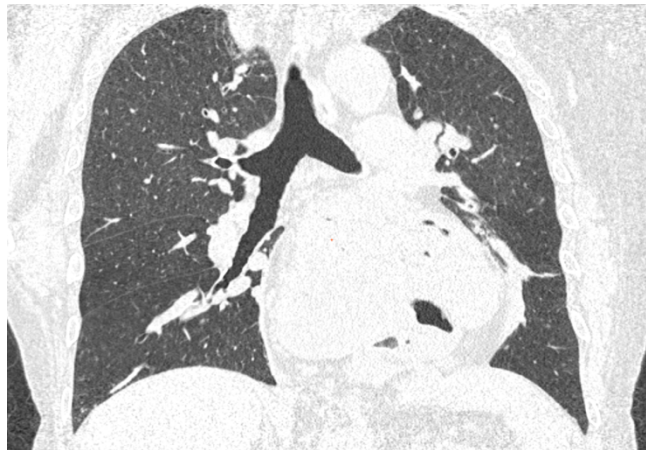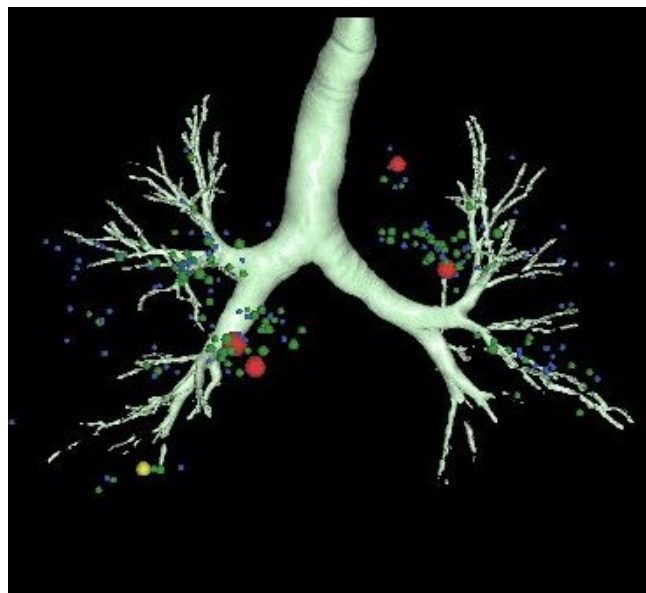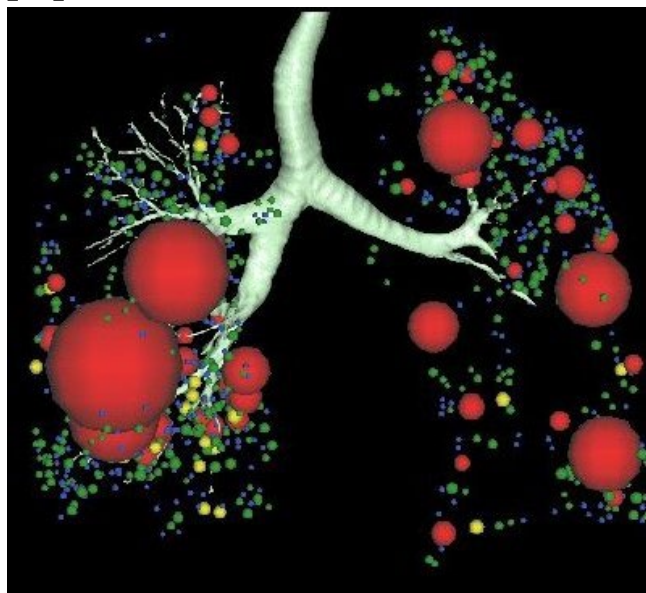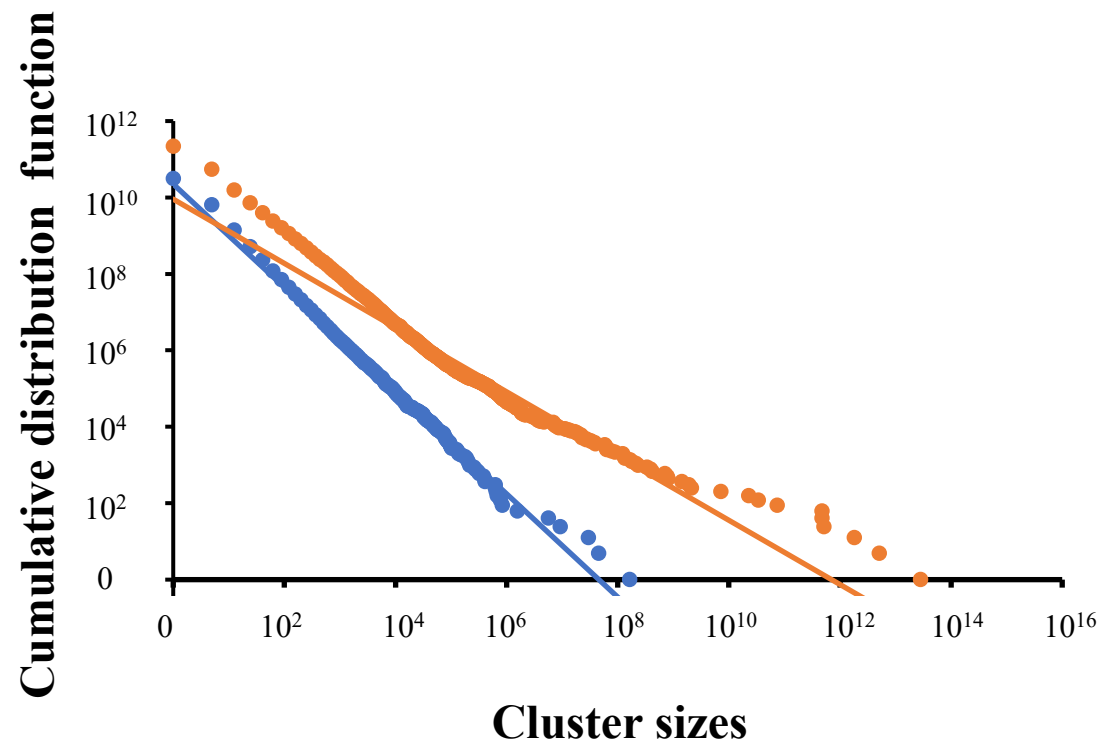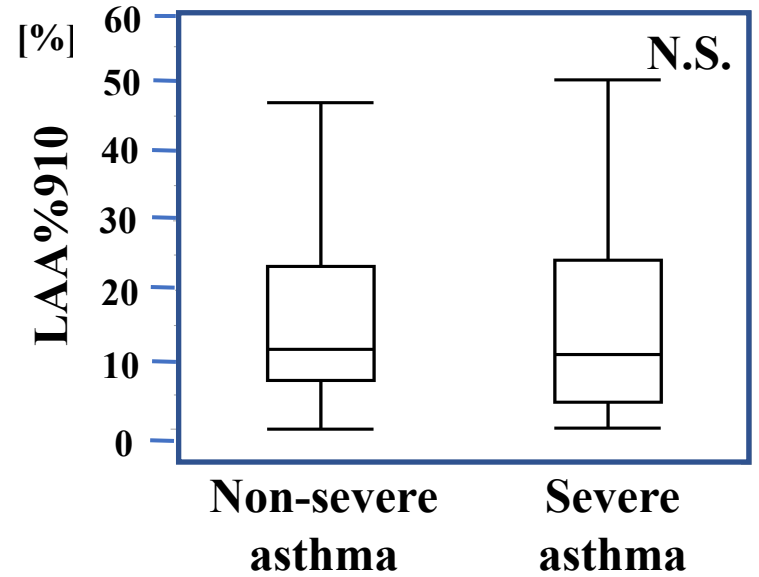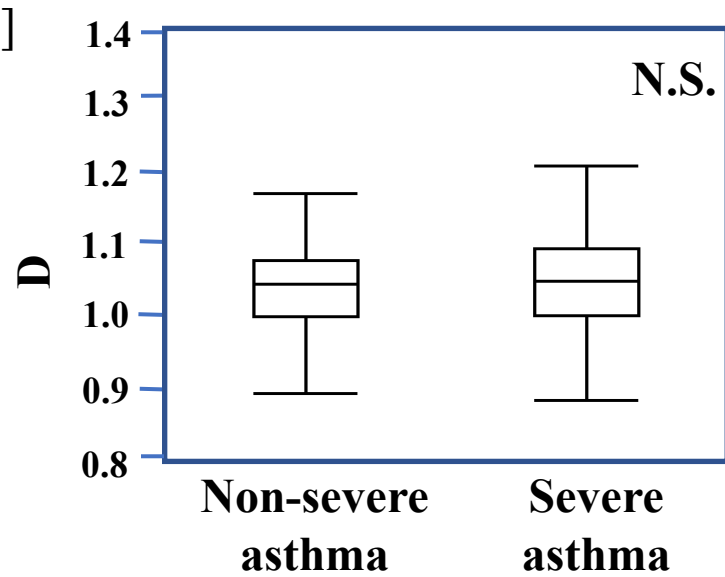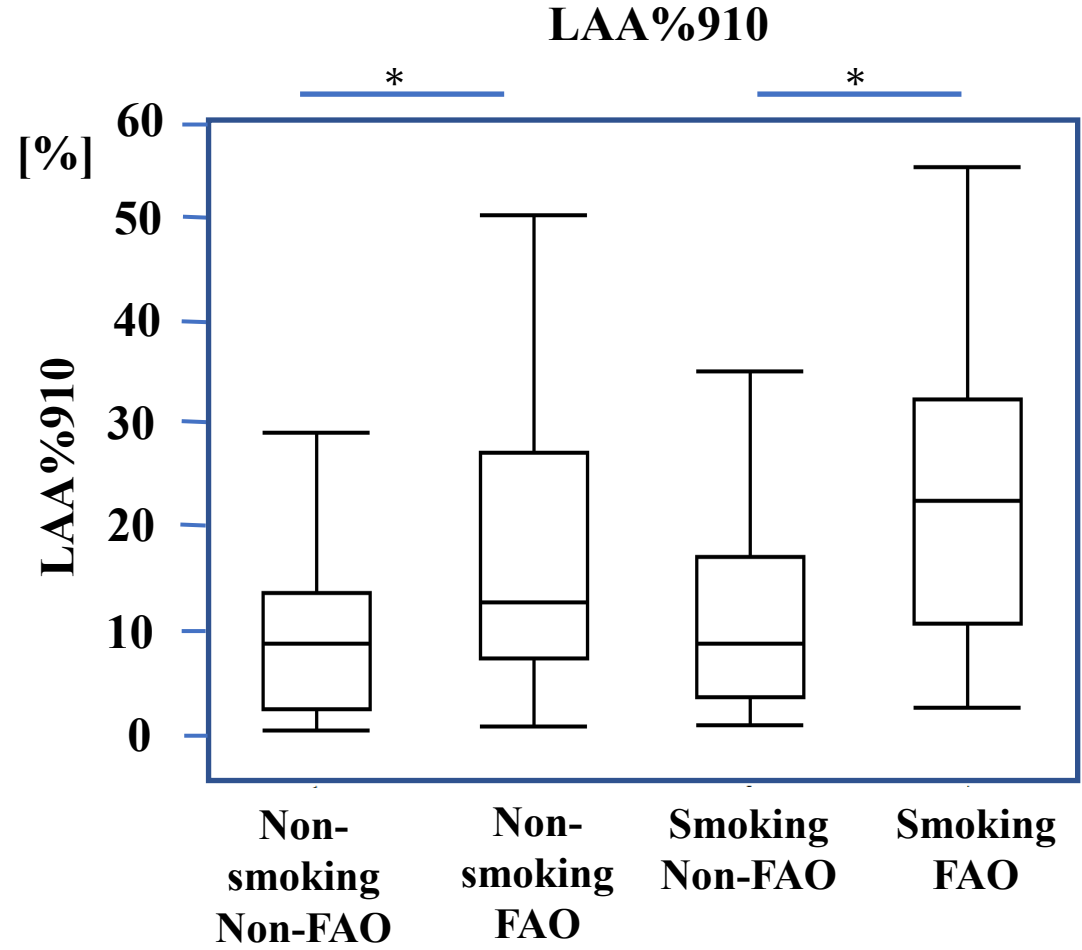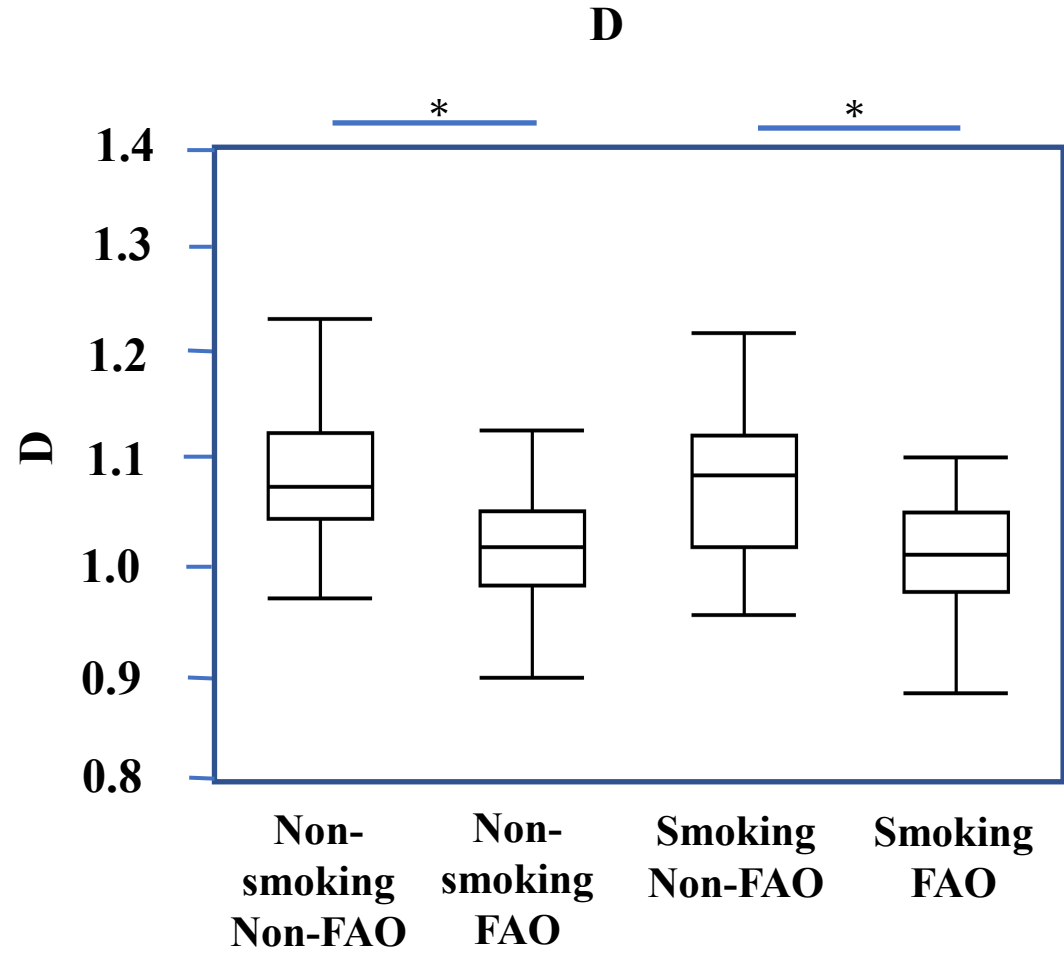
Figure 2
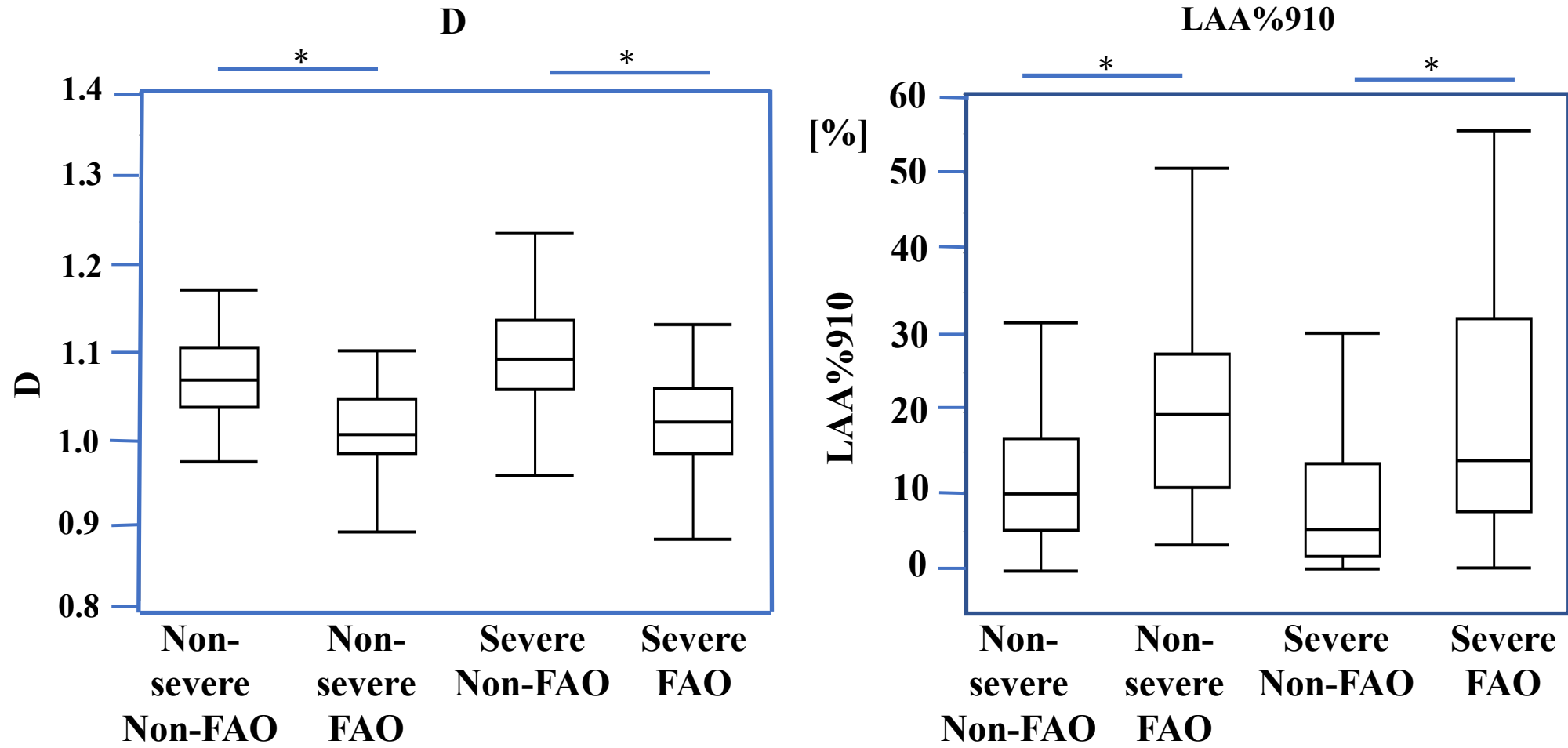
Figure 3.

Figure 4.

Figure E1.

Severe asthma	Non-severe asthma	COPD

Eligible for the initial study
N = 127

Eligible for the initial study
N = 86

Patients who underwent exams at
Hokkaido University Hospital on the fifth year visit
of the Hokkaido COPD cohort study N = 96

One who did not undergo
spirometry after
bronchodilation.

18 patients without CT data
analyzable for parenchymal and
airway indexes
5 patients who were examined by
a different CT scanner

Post-bronchodilator FEV$_1$ (% of
predicted) was less than 50%

Eligible for the present study
N = 126

Eligible for the present study
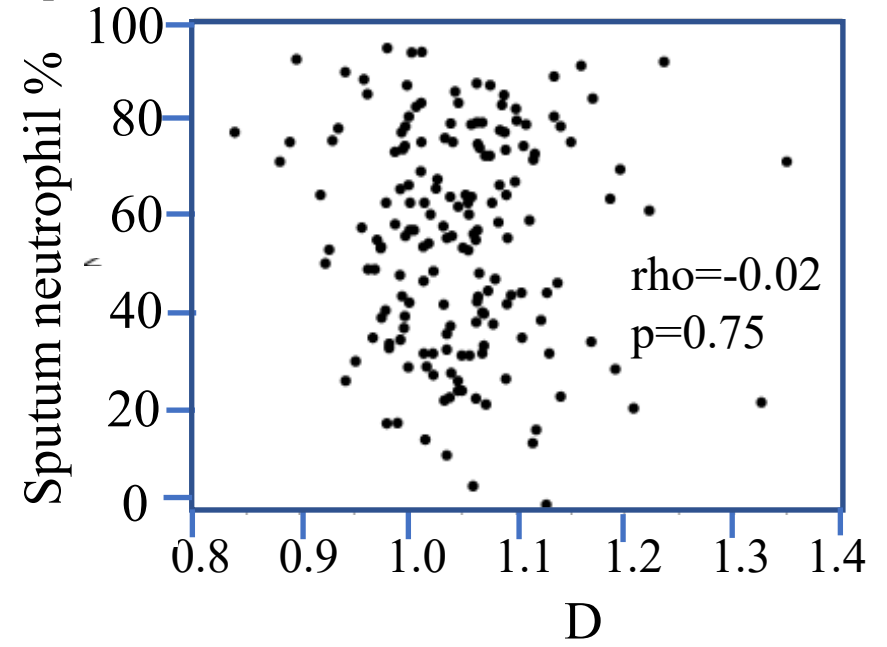N = 63

Eligible for the present study N = 42

Figure E2.

D

LAA%910

Figure E3