



Title	Combined assessment of pulmonary arterial enlargement and coronary calcification predicts the prognosis of patients with chronic obstructive pulmonary disease
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Citation	Respiratory medicine, 185, 106520 https://doi.org/10.1016/j.rmed.2021.106520
Issue Date	2021-08
Doc URL	http://hdl.handle.net/2115/86503
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1 **Combined assessment of pulmonary arterial enlargement and coronary calcification**
2 **predicts the prognosis of patients with chronic obstructive pulmonary disease**

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18

19 **Online data supplement**

20

21 **Supplementary Method: CT scanners and technical parameters**

22 **Hokkaido COPD cohort study**

23 Chest CT scans were administered in the supine position, with breath held at full
24 inspiration. No patient received intravenous contrast medium. The CT scanners and slice
25 thickness used in this study were as follows: Somatom plus Volume Zoom (Siemens,
26 Germany), 1.25 mm; Aquilion Multi TSX-101A/2A, 0.5 mm, TSX-101A/4E, 10 or 2 mm,
27 TSX-101A/6A, 0.5 mm, X Force TSX-011A/6A, 0.5 mm, X Vigor SS TSX-012A/4B, 10
28 or 2 mm (Toshiba, Japan); MX-8000/ID16 (Philips, Netherlands), 1 mm. Other technical
29 parameters were as follows; 1mm collimation, 120-140 kV, 75-350 mA, 0.75-1 s for
30 scanning time, and 1-2 mm thickness.

31

32 **Kyoto University cohort**

33 All CT images with a 0.5 mm slice thickness at full inspiration were obtained using an
34 Aquilion 64 scanner (Toshiba, Japan) with the use of 0.5 mm collimation, a scan time of
35 500 ms, 120 kVp and automatic exposure control, and reconstructed using a sharp
36 algorithm (kernel FC56).

37

38

39 **Supplementary Table 1 Annual change in post-bronchodilator forced expiratory**
 40 **volume in one second according to quartile groups in each cardiovascular finding in**
 41 **the discovery cohort patients**

42

	Number of participants	Annual decline in FEV ₁ , mL/year (SD)	<i>P</i> value
PA diameter			0.77
Q1	40	-30.1 (20.8)	
Q2	46	-25.3 (27.3)	
Q3	43	-30.4 (23.9)	
Q4	43	-28.9 (28.9)	
PA:A ratio			0.93
Q1	42	-29.7 (20.5)	
Q2	44	-28.3 (25.2)	
Q3	44	-29.7 (25.7)	
Q4	42	-26.7 (24.6)	
CACS			0.38
Q1	32	-25.5 (25.0)	
Q2	33	-34.8 (24.0)	
Q3	33	-26.7 (24.6)	
Q4	33	-30.7 (20.1)	

43 Data are shown as the mean (SD). Q1-4 show quartile groups according to the quartiles of
 44 distribution of each index. (Q1, <25th percentile; Q2, 25th percentile to ≤50th percentile; Q3,
 45 50th percentile to ≤75th percentile; and Q4, >75th percentile).

46 Comparisons between groups were conducted using Kruskal-Wallis test.
47 CACS, coronary artery calcium score; FEV₁, forced expiratory volume in one second; PA,
48 pulmonary artery; PA:A ratio, the ratio of the diameter of the pulmonary artery to the
49 diameter of the aorta.
50

51 **Supplementary Table 2 Multivariate analysis of exacerbation and mortality between**
 52 **participants with the increase in the PA:A ratio and/or CACS and those without them**
 53 **in the discovery and validation cohorts**

54

	Discovery cohort	Validation cohort
5-year exacerbation		
Prescription change	1.30 (0.72-2.34)	1.09 (0.72-1.67)
Admission	0.93 (0.34-2.47)	NA*
10-year mortality		
All-cause	1.89 (1.09-3.28)	4.97 (1.94-16.83)
Respiratory diseases	1.90 (0.81-4.48)	NA*
Cardiovascular diseases	8.16 (1.57-62.53)	NA*

55 Data are shown as hazard ratio (95% confidence intervals) of the subjects with the increase
 56 in the PA:A ratio and/or CACS compared to those with neither of them, adjusted by age,
 57 sex, body mass index, and %forced expiratory volume in one second. The increase in the
 58 PA:A ratio and CACS was defined as PA:A ratio >0.867 (75th quartile in the discovery
 59 cohort) and CACS >440.8 (75th quartile in the discovery cohort), respectively.

60 * NA, not assessed.

61 CACS, coronary artery calcium score; PA:A ratio, the ratio of the diameter of the
 62 pulmonary artery to the diameter of the aorta.

63

64 **Supplementary Table S3 Multivariate analysis of exacerbation and mortality**
65 **according to elevation of cardiovascular risk score (score 1 or 2 vs. 0) in the discovery**
66 **cohort**
67

	5-year exacerbation		10-year mortality		
	Prescription change	Admission	All-cause	Respiratory diseases	CVD
Model 1 (+ %Kco)*	1.24 (0.62- 2.30)	1.11 (0.40- 3.03)	1.82 (1.04- 3.24)	2.83 (1.13- 7.78)	4.08 (0.72- 29.64)
Model 2 (+ %LAV)†	1.17 (0.62- 2.15)	1.14 (0.41- 3.11)	2.03 (1.16- 3.63)	3.17 (1.25- 8.81)	3.27 (0.57- 26.66)
Model 3 (+ Total SGRQ score)	1.08 (0.58- 1.97)	1.05 (0.39- 2.83)	1.83 (1.06- 3.21)	3.06 (1.28- 8.14)	2.33 (0.49- 12.73)
Model 4 (+ Any CVD)	1.18 (0.57- 2.28)	1.10 (0.40- 2.93)	1.87 (1.08- 3.30)	3.12 (1.30- 8.32)	2.06 (0.41- 11.53)
Model 5 (+ IHD)	1.10 (0.59- 2.00)	1.10 (0.41- 2.93)	1.85 (1.07- 3.25)	2.97 (1.24- 7.91)	2.32 (0.49- 12.57)
Model 6 (+ Diabetes)	1.03 (0.54- 1.90)	1.01 (0.35- 2.75)	1.91 (1.09- 3.36)	3.33 (1.38- 8.85)	2.79 (0.58- 15.27)
Model 7 (+ Smoking index)	1.06 (0.57- 1.95)	1.05 (0.39- 2.81)	1.84 (1.06- 3.23)	3.21 (1.33- 8.54)	1.94 (0.40- 10.76)
Model 8 (+ Current smoking)	1.03 (0.55- 1.87)	0.97 (0.35- 2.63)	1.78 (1.03- 3.12)	2.66 (1.09- 7.15)	2.28 (0.48- 12.31)

68 Data are shown as hazard ratio (95% confidence intervals), adjusted by age, sex, body
69 mass index, %forced expiratory volume in one second, and each confounder described in
70 the table. * N = 127, † N = 126.

71 CVD, cardiovascular diseases; IHD, ischemic heart diseases; Kco, carbon monoxide
72 transfer coefficient; LAV, low attenuation regions over total lung; SGRQ, St. George's
73 Respiratory Questionnaire

74

75 **Supplementary Table 4 Multivariate analysis of exacerbation and mortality**
76 **according to elevation of cardiovascular risk score (score 1 or 2 vs. 0) in the**
77 **validation cohort**

78

	5-year exacerbation (Prescription change)	10-year mortality (All-cause)
Model 1 (+ %Kco)*	1.17 (0.75-1.86)	3.51 (1.47-9.82)
Model 2 (+ %LAV)	1.15 (0.74-1.82)	3.75 (1.61-10.30)
Model 3 (+ Total SGRQ score)†	1.14 (0.72-1.84)	3.09 (1.26-8.73)
Model 4 (+ Any CVD)	1.14 (0.66-1.86)	3.66 (1.58-10.02)
Model 5 (+ IHD)	1.15 (0.74-1.82)	3.67 (1.58-10.02)
Model 6 (+ Diabetes)	1.12 (0.64-2.13)	3.65 (1.57-9.95)
Model 7 (+Smoking index)	1.18 (0.76-1.86)	3.77 (1.62-10.33)
Model 8 (+Current smoking)	1.15 (0.75-1.82)	3.59 (1.59-9.81)

79 Data are shown as hazard ratio (95% confidence intervals), adjusted by age, sex, body
80 mass index, %forced expiratory volume in one second, and each confounder described in
81 the table. * N = 126, †N=121.

82 Kco, carbon monoxide transfer coefficient; LAV, low attenuation regions over total lung;

83 SGRQ, St. George's Respiratory Questionnaire; CVD, cardiovascular diseases; IHD,

84 ischemic heart diseases.

85

86

87 **Figure legends**

88

89 **Supplementary Fig. 1. Flow chart for subject selection in the discovery cohort**

90 CACS, coronary artery calcium score; COPD, chronic obstructive pulmonary disease; CT,

91 computed tomography; GOLD, Global Initiative for Chronic Obstructive Lung Disease;

92 PA, pulmonary artery; PA:A ratio, the ratio of the diameter of the pulmonary artery to the

93 diameter of the aorta

94

95 **Supplementary Fig. 2. Flow chart for subject selection in the validation cohort**

96 CACS, coronary artery calcium score; CT, computed tomography; PA, pulmonary artery;

97 PA:A ratio, the ratio of the diameter of the pulmonary artery to the diameter of the aorta

98

99 **Supplementary Fig. 3. Kaplan–Meier curves of time to first exacerbation and**

100 **mortality between participants with the increase in the PA:A ratio and/or CACS and**

101 **those without them the in the discovery and validation cohorts**

102 (A) 5-year exacerbation, (B) 10-year mortality. The increase in the PA:A ratio and CACS

103 was defined as PA:A ratio >0.867 (75th quartile in the discovery cohort) and CACS >440.8

104 (75th quartile in the discovery cohort), respectively. In the discovery cohort, the

105 participants with the increase in the PA:A ratio and/or CACS were associated with neither

106 exacerbation free period nor survival period compared to those with neither of them. In the

107 validation cohort, subjects with the increase in the PA:A ratio and/or CACS had worse

108 rates of all-cause mortality (log-rank, $P = 0.002$), whereas exacerbation free period was

109 comparable among groups.

110 CACS, coronary artery calcium score; PA:A ratio, the ratio of the diameter of the

111 pulmonary artery to the diameter of the aorta.

112

113 **Supplementary Fig. 4. Kaplan–Meier curves of mortality from respiratory disease**
114 **and cardiovascular disease according to cardiovascular risk score in the discovery**
115 **cohort**

116 (A) 10-year mortality from respiratory disease, (B) 10-year mortality from cardiovascular
117 disease. CR score was determined according to the distributions of measurement value in
118 the discovery cohort, consisting of pulmonary artery domain (0: the diameter of pulmonary
119 artery ≤ 29.5 mm or 75th percentile, 1: the diameter of pulmonary artery > 29.5 mm) and
120 coronary domain (0: coronary artery calcium score ≤ 440.8 or 75th percentile, 1: coronary
121 artery calcium score > 440.8), ranging from 0 to 2. The subjects with a score of 1 or more
122 had worse rates of mortality from respiratory disease (log-rank, $P = 0.003$), whereas rates
123 of mortality from cardiovascular disease was comparable among groups.

124 CR score, cardiovascular risk score.

125

126 **Supplementary Fig. 5. Kaplan–Meier curves of time to first exacerbation and**
127 **mortality according to quartile groups of each cardiovascular finding in the**
128 **validation cohort**

129 (A) 5-year exacerbation, (B) 10-year mortality. Q1-4 show quartile groups according to the
130 quartiles of distribution for each index assessed by the subjects of discovery cohort: in PA
131 diameter, Q1 (< 23.6 mm or 25th percentile), Q2 (23.6 to ≤ 26.0 mm or 50th percentile), Q3
132 (26.0 to ≤ 29.5 mm or 75th percentile), and Q4 (> 29.5 mm); in PA:A ratio, Q1 (< 0.701 or
133 25th percentile), Q2 (0.701 to ≤ 0.777 or 50th percentile), Q3 (0.777 to ≤ 0.867 or 75th
134 percentile), and Q4 (> 0.867); and in CACS, Q1 (< 5.3 or 25th percentile), Q2 (5.3 to ≤ 64.6
135 or 50th percentile), Q3 64.6 to ≤ 440.8 or 75th percentile), and Q4 (> 440.8). Higher CACS
136 quartiles were associated with development of exacerbation (log-rank, $P = 0.02$) and all-

137 cause mortality (log-rank, $P = 0.02$).

138 CACS, coronary artery calcium score; PA, pulmonary artery; PA:A ratio, the ratio of the

139 diameter of the pulmonary artery to the diameter of the aorta.

140

141