Associations of CT evaluations of antigravity muscles, emphysema and airway disease with longitudinal outcomes in patients with COPD

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ABSTRACT

Multiple CT indices are associated with disease progression and mortality in patients with COPD, but which indices have the strongest association remain unestablished. This longitudinal 10-year observational study (n=247) showed that the emphysema severity on CT is more closely associated with the progression of airflow limitation and that a reduction in the cross-sectional area of erector spinae muscles (ESM_{CSA}) on CT is more closely associated with mortality than the other CT indices, independent of patient demographics and pulmonary function. ESM_{CSA} is a useful CT index that is more closely associated with long-term mortality than emphysema and airway disease in patients with COPD.

COPD, characterised by airflow limitation, is associated with high morbidity and mortality.[1] Inspiratory chest CT is used to detect lung cancer and evaluate airway disease, emphysema and extrapulmonary abnormalities in patients with COPD.

CT studies have shown that emphysema severity, assessed as the low attenuation volume percentage (LAV%), is associated with the progression of airflow limitation and mortality.[1 2] The fractal dimension of low attenuation clusters (fractal D) that characterises the heterogeneity in sizes of emphysematous regions is more closely associated with exacerbation than the LAV%.[3] Regarding airway disease, the wall area percentage (WA%) is associated with chronic bronchitis symptoms, and the total airway count (TAC) predicts lung function decline[4] ; moreover, the airway to lung volume ratio (AWV%) is associated with airflow limitation and air trapping, independent of the TAC.[5] The loss of skeletal muscles is an extrapulmonary COPD feature that can be estimated as the reduction in the cross-sectional area of the erector spinae and pectoralis muscles (ESM_{CSA} and PM_{CSA}). The ESM_{CSA} and PM_{CSA} are associated with poor prognoses in patients[6] with COPD and non-COPD smokers,[7] respectively. Nonetheless, which CT indices have relatively stronger associations with disease progression and mortality remain unestablished.

This study analysed data from a single-centre prospective observational study to test whether the ESM_{CSA} and PM_{CSA} affect long-term COPD outcomes more strongly than airway disease and emphysema indices, independent of pulmonary function and demographics that are readily available in clinical practice. The ESM_{CSA} was measured on a CT image at the 12th thoracic vertebra (figure 1), and the PM_{CSA} was measured above the aortic arch.[6] The TAC, WA% of the segmental bronchus and AWV% were calculated to evaluate airway disease.[4 5] The LAV% and fractal D were calculated to evaluate emphysema.[3] To compare the relative impacts of the CT indices on FEV_1 decline and mortality, the CT indices were normalised by half of their SDs, as previously reported.[8] The normalised indices showed similar distribution patterns (figure 1C). FEV_1 measurements were repeated every 6–12 months for 5 years (total 1811 measurements/247 patients), and the annual FEV_1 decline was calculated using a linear mixed-effects model. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kyoto University (E182 and R0311-2). All participants provided written informed consent.

In total, 247 patients were enrolled from 2006 to 2012 (table 1). The median follow-up period was 3296 days, and 56 patients died. The mean (SD) FEV_1 decline was −34 (25) mL/year. In figure 2A, an increase in the LAV% only was significantly associated with an additional FEV_1 decline in univariable linear regression analyses, and an increase in the LAV% and decreases in the fractal D, TAC, PM_{CSA} and ESM_{CSA} were significantly associated with an increased HR for mortality in univariable Cox proportional hazards models. Figure 2B shows the results of multivariable linear regression analyses and Cox proportional hazards models that adjusted for age, sex, body mass index, mMRC dyspnoea scale, FEV_1 and diffusion capacity. An increase in the LAV% was associated with a larger FEV_1 decline (additional decline (95% CI) = −2.6 mL/year (−4.9, −0.3) per 4.65% increase) compared with the other CT indices, whereas reductions in the ESM_{CSA} were associated with poor prognoses (HR (95% CI) = 1.3 (1.1, 1.5) per 3.67 cm^2 reduction), with a stronger relationship than those of the other CT indices.

This is the first report to compare the relative impacts of various chest CT indices on lung function decline and mortality in COPD. The LAV% had the strongest association with the FEV_1 decline, and the ESM_{CSA} had the strongest association with mortality over 10 years after adjusting for clinical variables that are routinely collected in clinical COPD practice.

Previous studies confirmed the reproducibility of ESM_{CSA} measurements[6] and showed that a decreased ESM_{CSA} was associated with increased mortality in patients with COPD.[9] The present study extends this by showing that ESM_{CSA} is more strongly associated with mortality than emphysema

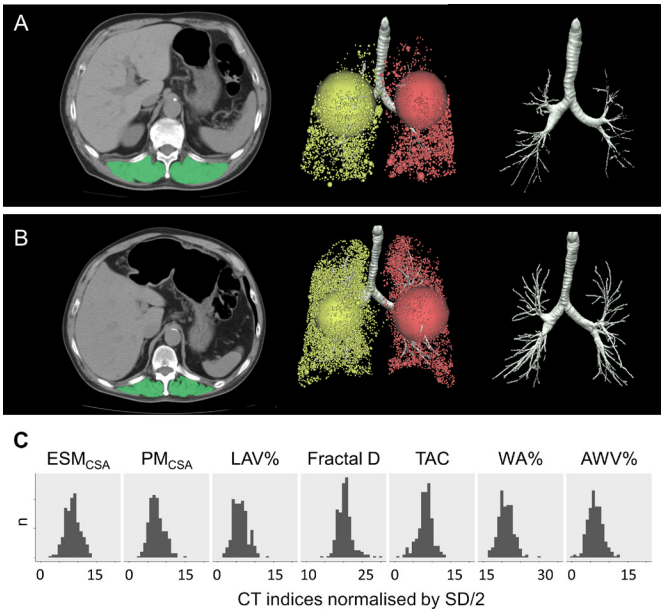

Figure 1 Two COPD cases with different cross-sectional areas of the erector spinae muscles on CT and distributions of normalised CT indices in all 247 cases. (A, B) The ESM_{CSA}, emphysema and airway indices were measured on CT scans in this study. The ESM_{CSA} was larger in case A than in case B (41.9 vs 21.0 cm^2). The TAC was also smaller in case A than in case B (178 vs 283), whereas the height (160 vs 163 cm), FEV_1 (1.12 vs 1.00 L), mMRC score (both 1) and LAV% (29.2 vs 29.5%) did not differ between the two cases. (C) Histogram of each CT index that was normalised by half of a SD. The distribution patterns, represented by the shape and range of histograms, were similar for all the normalised indices. This allowed a comparison of the relative impacts that are associated with a 1-normalised unit change. AWV%, airway to lung volume ratio; ESM_{CSA}, cross-sectional area of erector spinae muscles; fractal D, fractal dimension of low attenuation clusters; LAV%, low attenuation volume percentage; mMRC, modified Medical Research Council; PM_{CSA}, cross-sectional area of pectoralis muscles; TAC, total airway count; WA%, wall area percentage.

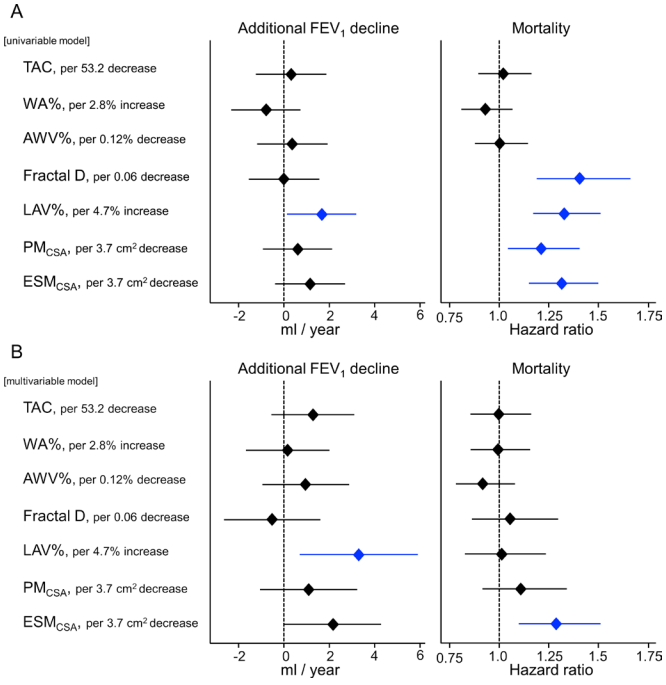

Figure 2 Univariable and multivariable analyses to compare the relative impacts of CT indices on lung function decline and mortality in patients with COPD (n=247). (A) Univariable models. (B) Multivariable models that included the CT index, age, sex, body mass index, smoking status, FEV_1 (% of predicted), diffusion capacity for carbon monoxide (% of predicted) and mMRC dyspnoea scale as explanatory variables. Diamonds and lines indicate the estimated magnitude of the association and 95% CI for each normalised CT index. AWV%, airway to lung volume ratio; ESM_{CSA}, cross-sectional area of erector spinae muscles; fractal D, fractal dimension of low attenuation clusters; LAV%, low attenuation volume percentage; mMRC, modified Medical Research Council; PM_{CSA}, cross-sectional area of pectoralis muscles; TAC, total airway count; WA%, wall area percentage.

and airway disease when demographics, dyspnoea and pulmonary function were considered. Since the loss of skeletal muscle mass is a prognostic factor in COPD and the PM_{CSA} can reflect the fat-free mass,[10] we speculate that the ESM_{CSA} could act as a surrogate for whole-body skeletal muscle mass and help predict the prognosis of COPD.

Table 1 Demographics of the study participants

N	247
Age, years	70.0 (8.4)
Sex (male:female)	224:23
Body mass index, kg/m^2	22.1 (2.9)
Smoking (pack-years)	64.8 (34.2)
FEV_1 (% predicted), %	61.8 (20.8)
FVC (% predicted), %	93.5 (16.7)
FEV_1/FVC, %	0.51 (0.1)
GOLD spirometric grade (1/2/3/4)	58/111/66/12
D_{LCO} (% predicted), %	54.7 (20.0)
mMRC (0/1/2/3/4)	70/115/54/8/0

D_{LCO}, diffusion capacity for carbon monoxide; GOLD, The Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council.

The association between the LAV% and FEV_1 decline presented here confirms that the emphysematous phenotype of COPD carries a high risk of lung function decline.[1] In contrast, the impact of the LAV% on mortality was confirmed in the univariable model but disappeared in the multivariable model. This might have been affected by the adjustment for diffusion capacity. However, even when diffusion capacity was excluded from the multivariable model, the ESM_{CSA} still had a stronger association with mortality (HR (95% CI)=1.30 (1.10, 1.54) per 3.67 cm^2 reduction) than the LAV% did (HR (95% CI)=1.20 (0.98, 1.38) per 4.65% increase). Furthermore, because FEV_1 and diffusion capacity can be measured without radiation exposure, the finding that the ESM_{CSA} had the strongest association with mortality independent of pulmonary function is clinically relevant.

The WA%, TAC and AWV% were not associated with FEV_1 decline or mortality. This finding is inconsistent with a previous finding showing an association between a lower TAC and a larger FEV_1 decline in patients with mild COPD.[5] This inconsistency might be due to differences in the inclusion criteria, as the present study included patients with all COPD severities.

This study has limitations. First, we did not assess physical activity, muscle strength or exercise capacity. Second, many patients did not use long-acting bronchodilators (LABDs) because the present study started in 2006. Whether LABDs affect the impact of CT indices on FEV_1 decline should be

further investigated. Third, the small numbers of female subjects and deaths may limit the generalisability of the findings.

In conclusion, the ESM_{CSA} is a useful imaging marker that is more closely associated with long-term mortality than emphysema and airway disease when assessing patients with COPD using demographics, dyspnoea, pulmonary function and CT findings.

Contributors NT designed the study, collected, analysed and interpreted the data, and wrote the manuscript. SS contributed to the study design, analysed and interpreted the data and assisted with editing the manuscript. KT contributed to the study design, data collection and interpretation of data analysis. AS and TO contributed to the study design and data analysis. SM contributed to data collection, analysed and interpreted the data and assisted with editing the manuscript. TH contributed to the data interpretation and support whole management of study. SS takes responsibility for the integrity of the project as a whole, from its inception to the manuscript's publication.

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REFERENCES

1 Vestbo J, Edwards LD, Scanlon PD, *et al*. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011;365:1184–92.
2 Haruna A, Muro S, Nakano Y, *et al*. CT scan findings of emphysema predict mortality in COPD. *Chest* 2010;138:635–40.
3 Shimizu K, Tanabe N, Tho NV, *et al*. Per cent low attenuation volume and fractal dimension of low attenuation clusters on CT predict different long-term outcomes in COPD. *Thorax* 2020;75:116–22.
4 Kirby M, Tanabe N, Tan WC, *et al*. Total airway count on computed tomography and the risk of chronic obstructive pulmonary disease progression. findings from a population-based study. *Am J Respir Crit Care Med* 2018;197:56–65.
5 Tanabe N, Sato S, Oguma T, *et al*. Associations of airway tree to lung volume ratio on computed tomography with lung function and symptoms in chronic obstructive pulmonary disease. *Respir Res* 2019;20:77.
6 Tanimura K, Sato S, Fuseya Y, *et al*. Quantitative assessment of erector spinae muscles in patients with chronic obstructive pulmonary disease. novel chest computed Tomography-derived index for prognosis. *Ann Am Thorac Soc* 2016;13:334–41.
7 Diaz AA, Martinez CH, Harmouche R, *et al*. Pectoralis muscle area and mortality in smokers without airflow obstruction. *Respir Res* 2018;19:62.
8 Waschki B, Kirsten A, Holz O, *et al*. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011;140:331–42.
9 Tanimura K, Sato S, Sato A, *et al*. Accelerated loss of antigravity muscles is associated with mortality in patients with COPD. *Respiration* 2020;99:298–306.
10 McDonald M-LN, Diaz AA, Ross JC, *et al*. Quantitative computed tomography measures of pectoralis muscle area and disease severity in chronic obstructive pulmonary disease. A cross-sectional study. *Ann Am Thorac Soc* 2014;11:326–34.