

Validation of the Lower Limit of Normal Diffusing Capacity for Detecting Emphysema

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Key Words

Validation · Lower limit of normal · Diffusing capacity · Emphysema · Chronic obstructive pulmonary disease

Abstract

Background: Diffusing capacity for carbon monoxide (D_{LCO}) has been regarded as reliable for detecting emphysema. The lower 5th percentile of the reference population has been used as the lower limit of normal (LLN) for D_{LCO} , without clinical validation. **Objectives:** We performed this study to validate the LLN for D_{LCO} and to determine the optimum cutoff LLN value for detecting emphysema. **Methods:** A total of 197 COPD patients and 103 healthy adult subjects were included. COPD patients with emphysema were defined as COPD patients in whom volumetric CT showed that the volume fraction of the lung at less than –950 Hounsfield units at full inspiration was more than 15%. All other COPD patients were defined as COPD patients without emphysema. All measured D_{LCO} values were transformed to estimates of refer-

ence population percentiles. ROC curve analysis was used to validate and to determine the optimum cutoff percentile value as the LLN for D_{LCO} . **Results:** Of the 197 COPD patients, 126 were classified as having emphysema and 71 as without emphysema. On ROC curve analysis, the lower 5th percentile used as the LLN for D_{LCO} had a sensitivity of 68.3% and a specificity of 98.1% to differentiate COPD patients with emphysema from healthy subjects. The lower 9th percentile was the best LLN cutoff value for detecting COPD patients with emphysema. **Conclusion:** The lower 5th percentile of the reference population may not be the best LLN cutoff value for D_{LCO} for detecting emphysema.

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Introduction

COPD is a principal cause of death in most countries and COPD prevalence is increasing [1, 2]. As none of the existing medications for COPD have been shown to modify the long-term decline in lung function, early detection and intervention is currently the best approach to reducing the burden of COPD. Among patients with COPD, those with emphysema have the lowest survival rate and the highest rate of pulmonary function decline [3]. Therefore, it is clinically important to detect emphysema during diagnostic workup of COPD patients. In patients with airflow obstruction, measurements of diffusing capacity for carbon monoxide (D_{Lco}) are regarded as reliable for distinguishing patients with emphysema from those with diseases of the airway alone (asthma or chronic bronchitis) [4]. D_{Lco} is usually decreased in patients with emphysema because of a loss of surface area of the alveolar-capillary membrane, whereas patients with asthma or chronic bronchitis generally do not have a decreased D_{Lco} [5–7]. Although D_{Lco} can be considered as a screening test to detect clinically unsuspected emphysema [8], the D_{Lco} test is apparently not adequately sensitive to detect emphysema because some patients with normal D_{Lco} values have shown clinically significant emphysema [9, 10].

In some pulmonary laboratories, D_{Lco} levels of less than 80% of the predicted value has been defined as abnormal. However, this cutoff value has no statistical basis [11]. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have recommended that the lower 5th percentile, or 95% confidence limit, of the reference population be used as the lower limit of normal (LLN) for pulmonary function parameters including D_{Lco} [4, 12]. Such cutoff values allow 5% false-positive diagnostic rates, which are considered clinically acceptable. This statistical definition of abnormality, however, is somewhat arbitrary [13]. Clinically, the lower 5th percentile may not be the best cutoff value of LLN for D_{Lco} because neither the sensitivity nor the false-negative rate, which is clinically more important in screening tests, have been considered.

We therefore attempted to validate the LLN for D_{Lco} and to determine the optimum LLN cutoff value for detecting emphysema in patients with COPD.

Materials and Methods

Study Subjects

Our study consisted of 197 COPD patients and 103 healthy adults. The COPD patients were selected from the Korean Ob-

structive Lung Disease (KOLD) cohort, into which patients with COPD or asthma had already been recruited from the pulmonary clinics of 11 hospitals in South Korea from August 2005 to April 2008. The inclusion criteria for the KOLD cohort have been described elsewhere [14, 15]. COPD was diagnosed based on smoking history (more than 10 pack-years) and the presence of airflow limitation that was not fully reversible [post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) <70%]. COPD patients with emphysema were defined as COPD patients in whom volumetric CT showed that the volume fraction of the lung at less than –950 Hounsfield units (HU) at full inspiration was more than 15% [16, 17]. Healthy adult subjects older than 20 years were recruited. Healthy subjects were defined as those who had no smoking history, normal chest X-ray results, no previous respiratory or cardiac disease history, and no chest surgery history. This study was approved by the institutional review boards of all 11 hospitals, and each patient or subject provided written informed consent.

Pulmonary Function Tests

Spirometry was performed as recommended by the ATS/ERS using a Vmax22 instrument (SensorMedics, Yorba Linda, Calif., USA) or a PFDX machine (MedGraphics, St. Paul, Minn., USA) [18]. D_{Lco} was measured by the single-breath method using a Vmax229D instrument (SensorMedics) or a Masterlab Body (Jaeger, Würzburg, Germany), following the ATS/ERS protocol recommendations [19]. The quality control for the 2 pieces of equipment had been performed with gas-analyzer zeroing before each measurement, with a volume test every day, and also with the testing of biologic controls every month. The predicted values of D_{Lco} and D_{Lco} /alveolar volume (V_A) were calculated from Park's equation formulated using data from a healthy Korean population [20]. Estimates of the lower 5th percentile and other percentiles of D_{Lco} were calculated from predicted values on the assumption that individually measured D_{Lco} values would show a distribution close to gaussian. The ATS recommends that normal ranges should be based on calculated 5th percentiles, whereas estimates of the lower 5th percentiles based on predicted values (the -1.645σ criterion) are acceptable for parameters with distributions that are close to gaussian [12].

Computed Tomography

Volumetric CT scans were performed on all patients using 16-slice multidetector CT scanners including the Somatom Sensation 16 (Siemens Medical Systems, Erlangen, Germany), the GE Lightspeed Ultra (General Electric Healthcare, Milwaukee, Wisc., USA), and the Philips Brilliance 16 (Philips Medical Systems, Best, The Netherlands). Patients were scanned during suspended full inspiration and expiration in the supine position. CT parameters were: 16 × 0.75 mm collimation, 100 effective mA, and 140 kVp (Somatom Sensation 16); 16 × 0.625 mm, 300 mA, 140 kVp, pitch 0.938, and 0.5 sec/rotation (GE Lightspeed); and 16 × 0.75 mm, 133 mA, 140 kVp, pitch 1, and 0.75 sec/rotation (Philips 16). Each CT machine was calibrated for water using a standard phantom once per month (and after major maintenance) and for air daily. We obtained screening scans within 24 h after calibration. Acquired data were reconstructed using a standard algorithm with 0.625–0.8 mm thickness and 0.625–0.8 mm increments. Image data were stored in DICOM format. Using in-house software, images of the whole lung were extracted automatically, and the

Table 1. Characteristics of patients

	COPD patients with emphysema (n = 126)	COPD patients without emphysema (n = 71)	Healthy subjects (n = 103)
Gender (M:F)	122:4 ^a	68:3 ^a	38:65
Age, years	66.6 ± 7.0 ^a	65.1 ± 7.6 ^a	42.3 ± 14.4
BMI	21.9 ± 3.1 ^{a, b}	24.9 ± 3.8 ^a	23.2 ± 3.0
FEV ₁ , % predicted	43.9 ± 15.4 ^{a, b}	55.3 ± 14.1 ^a	87.7 ± 12.1
FVC, % predicted	72.2 ± 21.1 ^a	71.4 ± 21.2 ^a	91.8 ± 10.6
FEV ₁ /FVC, %	421.0 ± 9.9 ^{a, b}	52.7 ± 8.9 ^a	82.2 ± 6.3
D _{Lco} , % predicted	62.7 ± 21.7 ^{a, b}	96.9 ± 28.0	102.4 ± 14.0
D _{Lco} /V _A , % predicted	66.2 ± 20.8 ^{a, b}	93.6 ± 20.5	100.8 ± 13.5

^a p < 0.05 vs. healthy subjects; ^b p < 0.05 vs. COPD patients without emphysema.

attenuation coefficient of each pixel was measured and calculated. From the CT data, the volume fraction of the lung below -950 HU (V₉₅₀) was calculated automatically [14, 15].

Statistical Analysis

Baseline characteristics except gender ratio were expressed as means ± SD. Univariate analysis used χ^2 tests for categorical variables and one-way ANOVA for quantitative variables with Scheffe's test as a post-hoc test for multiple comparisons. Relationships between any 2 quantitative variables were assessed using Pearson's correlation analysis. All tests were performed employing the SPSS statistical package (SPSS version 12.0, SPSS, Chicago, Ill., USA), and values of p < 0.05 were considered statistically significant.

All measured D_{Lco} values were transformed to estimates of reference population percentiles using a standard normal table after calculating standardized residuals. The following formula was used: standardized residual = (x - μ)/ σ ; x = measured D_{Lco}, μ = predicted D_{Lco}, σ = residual standard deviation [11]. To validate LLNs determined by the lower 5th percentiles of reference populations, and to compare these LLNs with LLNs obtained with reference to other percentiles, ROC curves were constructed by plotting sensitivity versus 1 - specificity (MedCalc software v. 4.2, Broekstraat, Belgium). A cutoff value providing the best combination of sensitivity and specificity was determined. Next, we compared the sensitivities and specificities of LLNs determined by several cutoff values, including the lower 5th percentile, the 80% predicted, and the best cutoff percentile, as shown by ROC curve analysis.

Results

Among the 197 COPD patients, 190 were male and 7 female. Age and FEV₁ were 66.1 ± 7.2 years and 48.0 ± 15.9% predicted, respectively. We observed a moderate negative correlation between D_{Lco} (% predicted) and CT

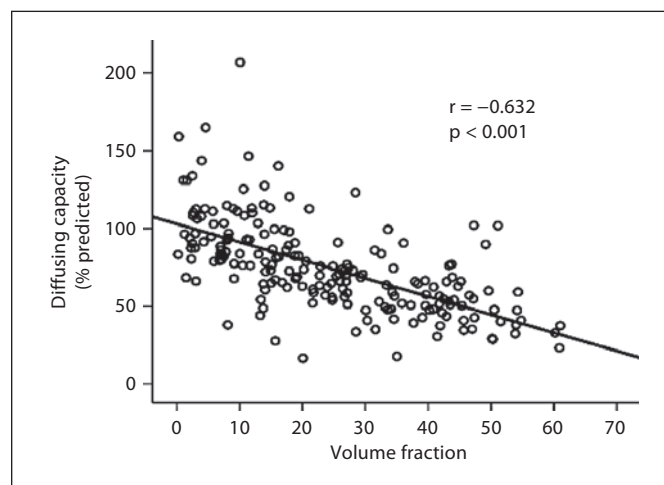


Fig. 1. Correlation between diffusing capacity (% predicted) and emphysema extent on CT (volume fraction of the lung below -950 HU at full inspiration).

emphysema extent (V₉₅₀) (fig. 1). Of the 197 COPD patients, 126 were classified as having emphysema and 71 as without emphysema. COPD patients with emphysema had significantly lower mean body mass index (BMI), FEV₁, FEV₁/FVC, D_{Lco}, and D_{Lco}/V_A values compared with COPD patients without emphysema and with healthy subjects (table 1). There were no significant differences in mean D_{Lco} and D_{Lco}/V_A values between COPD patients without emphysema and healthy subjects.

Of the 126 COPD patients with emphysema, 23 had D_{Lco} values more than 80% predicted and 40 had D_{Lco} values more than the lower 5th percentile of the reference population (fig. 2).

On ROC curve analysis, the lower 5th percentile used as the LLN for D_{Lco} had a sensitivity of 68.3% and a specificity of 84.5% to differentiate COPD patients with emphysema from COPD patients without emphysema, and a sensitivity of 68.3% and a specificity of 98.1% to differentiate COPD patients with emphysema from healthy subjects.

The lower 9th percentile was the best LLN cutoff value for D_{Lco} to differentiate COPD patients with emphysema from COPD patients without emphysema and from healthy subjects (fig. 3; table 2). The accuracy for differentiating COPD patients with emphysema from COPD patients without emphysema was 78.7% and the accuracy for differentiating COPD patients with emphysema from healthy subjects was 87.2%.

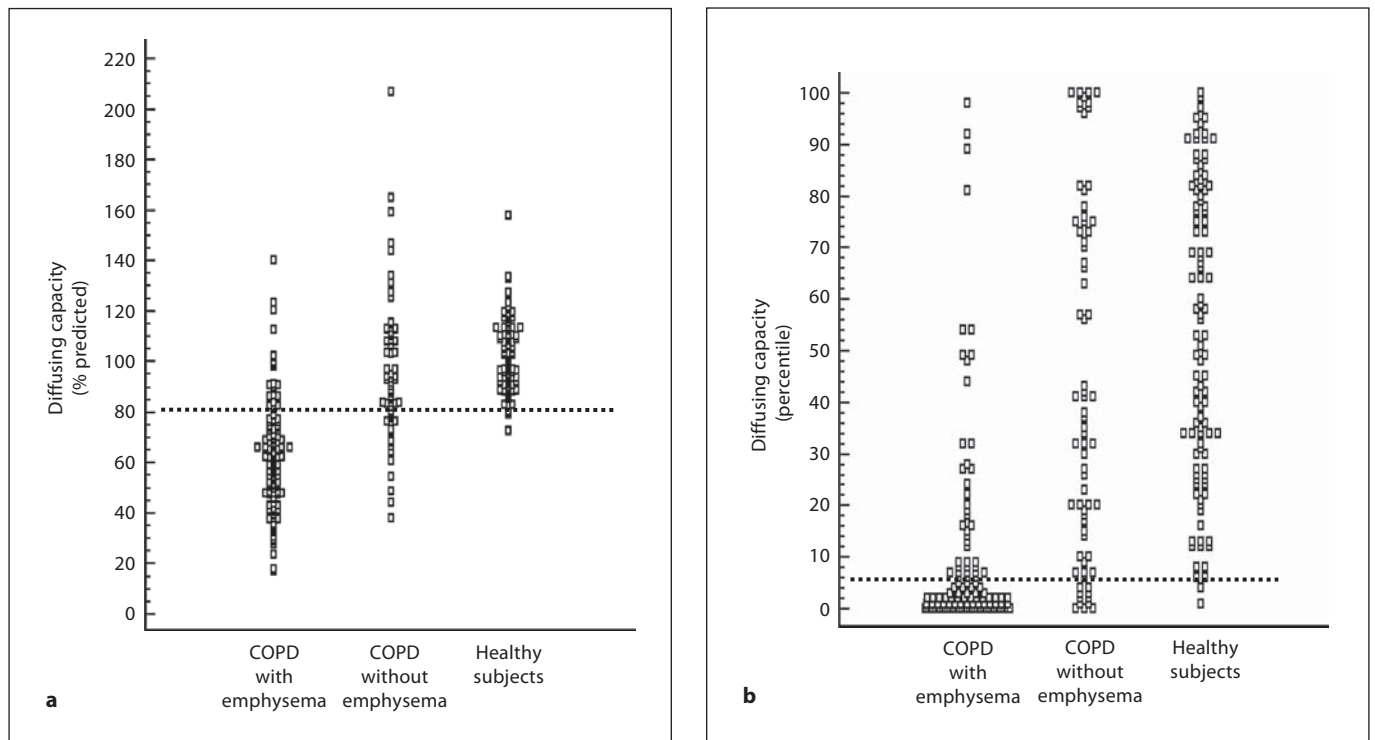


Fig. 2. Distribution of % predicted (**a**) and percentile (**b**) values of diffusing capacity in patients with COPD (with/without emphysema on CT) and healthy subjects. Dotted lines indicate 80% predicted (**a**) and lower 5th percentile (**b**).

Table 2. Ability of the 2 cutoffs to differentiate COPD patients with and without emphysema and COPD patients with emphysema from healthy subjects

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Lower 5th percentile				
With vs. without emphysema	68.3	84.5	88.7	60.0
With emphysema vs. healthy	68.3	98.1	97.7	71.6
Lower 9th percentile				
With vs. without emphysema	79.4	77.5	86.2	67.5
With emphysema vs. healthy	79.4	94.2	94.2	77.0

PPV = Positive predictive value; NPV = negative predictive value.

Discussion

We have shown here that the optimum cutoff value of the LLN of D_{Lco} , used to detect emphysema among patients with COPD may not be the lower 5th percentile of the reference population. To the best of our knowledge, this is the first clinical validation of a statistically defined LLN for D_{Lco} used to detect emphysema among patients with COPD. We have previously shown that an LLN for

D_{Lco} set at the lower 10th percentile was superior to an LLN defined with reference to the lower 5th percentile in detecting interstitial lung disease [21]. The results of these 2 studies indicate that statistically defining LLN for D_{Lco} as the lower 5th percentile may not be optimal for detecting emphysema or interstitial lung disease. Furthermore, these results indicate that the optimal LLN cutoff value should be determined by clinical validation, not merely statistically [22].

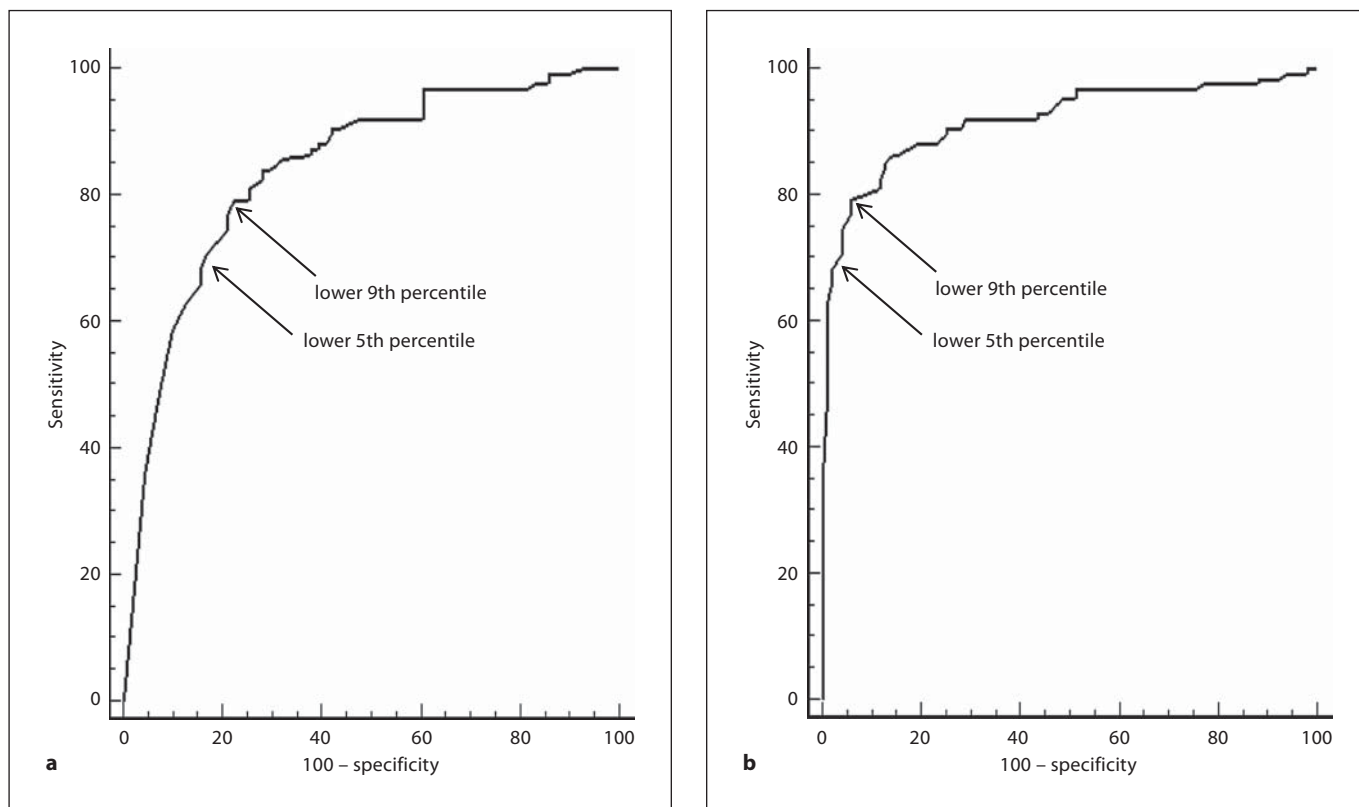


Fig. 3. ROC curves for percentile values of diffusing capacity used as lower limits of normal to detect COPD patients with emphysema versus COPD patients without emphysema (**a**: AUC = 0.84, SE = 0.03) and healthy subjects (**b**: AUC = 0.92, SE = 0.02).

COPD is the only leading cause of death that is increasing in prevalence worldwide [1, 2], and is widely under-diagnosed in the primary care setting [23]. Many seemingly healthy smokers were found to have emphysematous lesions on CT [24, 25]. Therefore, early diagnosis of emphysema is important for clinical and epidemiologic purposes. A low D_{Lco} can detect clinically unsuspected emphysema [8, 25] and is highly correlated with the degree of emphysema on lung CT scan [26, 27]. D_{Lco} measurement is rapid and simple, and can be considered to be a pulmonary function test used to screen for emphysema. In recognizing the clinical importance of the D_{Lco} test, the ATS and ERS have set test performance standards [19], and have recommended that the lower 5th percentile of the reference population should be used as the LLN for D_{Lco} [4]. However, we considered that this statistically defined LLN may be of limited clinical value in detecting emphysema because this LLN does not reflect the distribution of test results in patients with emphysema. Moreover, previous studies have reported that indi-

vidual patients may have significant emphysema but a normal D_{Lco} values [9, 10]. Although we included only symptomatic COPD patients in the present study, the lower 5th percentile of the reference population, when used as the LLN, showed relatively low sensitivity in detecting emphysema.

We defined the emphysema group using volumetric CT, although emphysema is conventionally diagnosed using pathologic criteria such as an 'abnormal permanent enlargement of the airspaces' [28]. Many studies have addressed the ability of CT to accurately quantify the extent and severity of pulmonary emphysema [27, 29, 30]. The density mask technique has been widely used for the quantification of emphysema, with the threshold for measuring emphysematous pixels varying from under -900 HU to less than -960 HU [27]. We utilized -950 HU as the threshold for detecting emphysema because previous CT pathologic correlations have shown that the use of this criterion correlated well with diagnoses employing macroscopic/microscopic measurements [31, 32]. In ad-

dition, a paired inspiratory/expiratory CT measurement study found that measurements between -900 HU and -950 HU indicated air trapping, whereas levels below -950 HU indicated emphysema [33]. Emphysema is considered present when more than 10% of pixels fall below the cutoff values of -910 or -920 HU, depending on slice thickness and the reconstruction algorithm employed [29]. We used 15% of V_{950} , as measured by volumetric multidetector CT, as a cutoff value to distinguish between emphysema and no-emphysema patients. This cutoff value of 15% was derived from measurements of V_{950} in 48 healthy nonsmokers in our hospital, which found that V_{950} ranged from 0.15 to 13.25%, with a mean of 4.66% (unpublished data). Thus, we were confident that V_{950} values less than 15% were compatible with no or trivial emphysema [16, 17]. We found that COPD patients with emphysema had significantly lower BMI, FEV₁, FEV₁/FVC, and D_{Lco} than COPD patients without emphysema and healthy adults. This was consistent with previous reports describing the characteristics of emphysematous phenotypes in COPD patients identified by high-resolution CT [16, 34].

Our study has 2 limitations. Firstly, relatively few numbers of females were included. Our study result may not be generalized to female COPD patients because previous studies have suggested that gender might have an impact upon COPD manifestations [35]. Secondly, we used 3 different multidetector CT scanners produced by different manufacturers. Thus, our emphysema index values may have included some errors because different

CT scanners employ distinct values of air density. However, no method correcting for differences between CT scanners has yet been established. Future studies are needed to devise a correction algorithm.

In conclusion, our findings indicate that the lower 5th percentile of the reference population may not be the best D_{Lco} cutoff value for D_{Lco} because this value had a low sensitivity for detecting COPD patients with emphysema.

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Conflict of Interest Statement

J.B.S. has been an investigator in a government-sponsored study (2006–2008, Korea Science and Engineering Foundation). Y.-M.O. has been an investigator in university-sponsored studies (University of Ulsan College of Medicine) and an industry-sponsored study (AstraZeneca Korea), and has participated as a speaker in scientific meetings organized and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca Korea, MSD Korea, and Boehringer Ingelheim). S.-D.L. serves as a consultant to GlaxoSmithKline and has participated as a speaker in scientific meetings organized and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca Korea, and Boehringer Ingelheim).

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