

Comparison of the Prevalence of Chronic Obstructive Pulmonary Disease Diagnosed by Lower Limit of Normal and Fixed Ratio Criteria

The Global Initiative of Chronic Obstructive Lung Disease (GOLD) guidelines define chronic obstructive pulmonary disease (COPD) in subjects with $FEV_1/FVC < 0.7$. However, the use of this fixed ratio may result in over-diagnosis of COPD in the elderly, especially with mild degree of COPD. The lower limit of normal (LLN) can be used to minimize the potential misclassification. The aim of this study was to evaluate the impact of different definitions of airflow obstruction (LLN or fixed ratio of FEV_1/FVC) on the estimated prevalence of COPD in a population-based sample. We compared the prevalence of COPD and its difference diagnosed by different methods using either fixed ratio ($FEV_1/FVC < 0.7$) or LLN criterion (FEV_1/FVC below LLN). Among the 4,816 subjects who had performed spirometry, 2,728 subjects met new ATS/ERS spirometry criteria for acceptability and repeatability. The prevalence of COPD was 10.9% (14.7% in men, 7.2% in women) by LLN criterion and 15.5% (21.8% in men, 9.1% in women) by fixed ratio of FEV_1/FVC among subjects older than 45 yr. The difference of prevalence between LLN and fixed ratio of FEV_1/FVC was even higher among subjects with age ≥ 65 , 14.9% and 31.1%, respectively. In conclusion, the prevalence of COPD by LLN criterion was significantly lower in elderly compared to fixed ratio of FEV_1/FVC . Implementing LLN criterion instead of fixed ratio of FEV_1/FVC may reduce the risk of over-diagnosis of COPD in elderly people.

Key Words : Pulmonary Disease, Chronic Obstructive; National Prevalence; Lower Limit of Normal; Spirometry

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Received : 27 November 2007

Accepted : 29 September 2008

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation which is not fully reversible. COPD is a leading cause of morbidity and mortality worldwide and is the only major disease that is continuing to increase in both prevalence and mortality (1-4). Since early detection and intervention is currently the best approach to reduce the economic and social burden of COPD, there has been a call for global strategies to assess the prevalence of COPD (5).

Spirometry is essential for diagnosis in COPD. The ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) is an acceptable indicator of the presence of airflow limitation. Unfortunately, there was no consensus on diagnostic criteria of COPD, every guidelines used their own diagnostic criteria recently (6-9). After the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was introduced in 2001, specific spirometric cut-point (e.g., post-bronchodilator $FEV_1/FVC < 0.7$) has been used for diagnosing COPD (1, 10).

A nationwide COPD prevalence survey in Korea in conjunction with the second Korean National Health and Nutri-

tion Examination Survey (Korean NHANES II) was conducted from 2001 to 2002. Using GOLD criterion for defining airflow limitation, 17.2% of Korean adults over the age of 45 yr had COPD and most of them had mild disease (11).

However, the FEV_1/FVC ratio decreases with age because the FEV_1 declines more rapidly with age than the FVC in normal subjects, so the FEV_1 percentage of predicted will decrease with age because of the shrinking denominator of the percentage of predicted index. Therefore, it is suggested that the use of fixed ratio may result in over-diagnosis of COPD in the elderly, especially with mild disease (12).

The Korean COPD prevalence survey showed that 35.0% of adults over the age of 65 yr and 41.4% over the age of 70 yr (11) proved to have COPD. Even though more than half of them belonged to mild degree of COPD, the figure seemed to be over-exaggerated in elderly. Therefore, we need to apply a new criterion to correct overwhelming higher prevalence of COPD in senior citizens. The lower limit of normal (LLN), based on the normal distribution, classify the bottom 5% of the healthy population as abnormal. When we use LLN criterion in the evaluation of FEV_1/FVC , it could be one of alternatives to minimize the potential misclassification (1,

13). The objective of this study was to compare the prevalence of COPD by using fixed ratio and LLN of FEV₁/FVC for the presence of airflow limitation.

MATERIALS AND METHODS

This study was performed as a part of a nationwide COPD prevalence survey. It was conducted in conjunction with the second Korean National Health and Nutrition Examination Survey (Korean NHANES II) from October 15, 2001 to January 20, 2002. Spirometry was performed by specially trained technicians who conformed to the 1994 American Thoracic Society (ATS) recommendations (11, 14). In 2005, ATS and European Respiratory Society (ERS) published a new statement on spirometry that changed the repeatability criteria (the difference between the largest and the next largest FEV₁) from ≤ 0.2 L to ≤ 0.15 L (15). So the acceptability and repeatability criteria of the spirometry in this study were adopted from the 2005 new ATS/ERS recommendations (15). A more detailed description of the nationwide COPD survey methodology and spirometric procedures has been previously published (11, 14).

Selection of new reference population

A reference equation for FEV₁/FVC was developed in the Korean NHANES II (14). But as we mentioned, the repeatability criterion of the spirometry was changed in the new ATS/ERS spirometry recommendations (15), a new reference equation for FEV₁/FVC was needed. The selection criteria of new reference population were similar to the previous study (14) except for the definition of the non-smoker. We defined the lifetime non-smoker as a subject who had never smoked (14). And the acceptability and repeatability criteria of the spirometry were adopted from the new ATS/ERS spirometry recommendations (15). Total 1,125 subjects met the selection criteria for new reference population. There were 183 male and 942 female in the new reference population.

New predictive equation for FEV₁/FVC and LLN of the FEV₁/FVC

A new prediction equation for FEV₁/FVC was made by linear regression analysis. The variables affecting the normal predicted values of the FEV₁/FVC for male and female were age and height. The new prediction equations were $125.77628 - 0.36304 \times \text{age (yr)} - 0.17146 \times \text{height (cm)}$ for Koreans male and $97.36197 - 0.26015 \times \text{age (yr)} - 0.01861 \times \text{height (cm)}$ for Koreans female.

The observed values of FEV₁/FVC were distributed normally, so the lower limits of the normal range (LLN) for FEV₁/FVC were calculated for each subject using the new reference equations. These were based on the predicted value minus

Table 1. New prediction equation of FEV₁/FVC%* in adult Koreans

	Equation	R ²	SEE
Male	$125.77628 - 0.36304 \times \text{Age} - 0.17146 \times \text{Ht}$	0.4309	5.35
Female	$97.36197 - 0.260154 \times \text{Age} - 0.01861 \times \text{Ht}$	0.2420	5.41

*Ratio, FEV₁/FVC \times 100%.

Ht, height in cm; R², coefficient of determination; SEE, standard error of the estimate.

1.645-times the standard error of the estimate (SEE) (16, 17) (Table 1).

Analysis

The new prediction equation from the present study was compared to the other prediction equations (14, 18-21). The differences between predictive values based on the prediction equations from the present study and others were divided by the predictive values from the present study or others and then multiplied by 100. The mean differences in percent were used to compare the equations.

The presence of airflow limitation was assessed by fixed ratio criterion and LLN criterion, each of which was defined as FEV₁/FVC less than 0.7 or LLN, respectively. COPD was defined as presence of airflow limitation in persons aged 45 or older (11).

The crude prevalence rates of airflow limitation for every 100 persons per each age group from the study population were obtained and they were post-stratified to the Korean population as estimated by the Bureau of the Census 2001 (22) to adjust for unequal probabilities of selection. Then the age adjusted standardized prevalence rates of airflow limitation were calculated for the age group ≥ 18 and ≥ 45 yr.

The two criteria of airflow limitation (fixed ratio and LLN) were compared in terms of the crude prevalence of airflow limitation and the age adjusted standardized prevalence of COPD.

RESULTS

Study populations

Total 4,816 subjects performed the spirometry. Among 4,816 subjects, 2,728 (men, 1,263, women, 1,465) subjects met the new ATS/ERS acceptability and repeatability criteria. The median age of the study population was 41 yr. The mean \pm SD FEV₁/FVC % was 79.4 ± 8.3 for men and 83.0 ± 6.8 for women. There were 1,093 subjects aged 45 yr or older who met the new ATS/ERS acceptability and repeatability criteria. For the entire study population, there were 789 current smokers (men, 738, women, 51). Table 2 described the characteristics of the study population according to the age group.

Table 2. Spirometry data of study population according to the age groups

Age (yr)	Subjects (No.)			FVC (L)*		FEV ₁ (L)*		FEV ₁ /FVC%*	
	Total	Male	Female	Male	Female	Male	Female	Male	Female
18-24	250	124	126	4.98±0.59	3.50±0.40	4.38±0.50	3.08±0.40	88.2±6.1	87.9±7.3
25-29	255	112	143	5.00±0.60	3.54±0.45	4.22±0.53	3.11±0.40	84.5±5.8	88.1±5.7
30-34	357	166	191	4.97±0.66	3.51±0.46	4.09±0.57	3.00±0.39	82.3±5.9	85.8±6.0
35-39	392	187	205	4.89±0.63	3.48±0.45	3.94±0.55	2.93±0.39	80.7±5.9	84.4±5.8
40-44	381	173	208	4.81±0.63	3.35±0.39	3.82±0.50	2.77±0.35	79.6±5.2	82.8±5.1
45-49	285	143	142	4.51±0.61	3.29±0.46	3.52±0.49	2.69±0.38	78.3±6.3	81.9±5.1
50-54	212	82	130	4.37±0.56	3.19±0.40	3.35±0.54	2.56±0.34	76.5±7.2	80.6±5.0
55-59	231	113	118	4.28±0.63	2.97±0.50	3.18±0.52	2.36±0.44	74.6±6.9	79.3±5.9
60-64	176	77	99	4.16±0.68	2.78±0.45	2.96±0.63	2.20±0.39	71.0±9.2	79.1±6.2
65-69	112	50	62	3.85±0.69	2.65±0.43	2.70±0.59	2.01±0.40	69.7±8.9	75.4±7.0
70-74	51	23	28	3.57±0.60	2.47±0.36	2.47±0.55	1.83±0.34	69.0±12.0	74.2±7.4
≥75	26	13	13	3.37±0.33	2.31±0.53	2.24±0.33	1.76±0.47	66.5±8.4	75.9±5.4
Total	2,728	1,263	1,465	4.65±0.73	3.27±0.53	3.70±0.74	2.76±0.52	79.4±8.3	83.0±6.8

*, mean ± SD.

Table 3. The difference between new predication equation and other equations

Reference	Male		Female	
	Difference* Mean (%)	Difference† Mean (%)	Difference* Mean (%)	Difference† Mean (%)
Crapo (18)	0.36	0.48	-0.84	-0.81
Knudson (19)	0.32	0.47	-1.13	-1.09
CHS (20)	-0.13	-0.11	0.98	0.99
BOND (21)	-0.29	-0.06	0.73	0.81
KNHANES II (14)	-0.82	-0.81	-0.19	-0.19

*100 × ((predicted value of present study - predicted value of the major equation) / predicted value of present study); †100 × ((predicted value of present study - predicted value of the major equation) / predicted value of the other study).

Comparison of new prediction equation of FEV₁/FVC with other prediction equations

We compared the new predication equation of the present study with other equations (18-21) and that of the Korean NHANES II (14). The mean differences of predictive values were less than 1% except the equation for the women of Knudson's study (19), which showed 1.09% difference (Table 3). The predictive values from the present study were slightly less than those from the original equation derived from the Korean NHANES II (14) for both men and women.

Crude prevalence rates of the airflow limitation by each criterion

Among the study population, total 240 subjects met LLN criterion for airflow limitation, whereas 186 subjects met fixed ratio criterion. Among Korean adults over age of 18 yr, the crude prevalence rate of airflow limitation was 8.7% (men 11.4%; women 6.3%) by using LLN criterion and 6.8% (men

Table 4. Crude prevalence rate of airflow obstruction by each criterion according to the age groups

Age (yr)	By Fixed ratio			By LLN		
	Total (%)	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)
18-24	1.6	0.8	2.4	8.4	6.5	10.3
25-34	1.5	2.2	0.9	7.8	10.1	6.0
35-44	3.2	5.0	1.7	7.0	10.0	4.4
45-54	5.8	9.3	2.9	8.0	9.8	6.6
55-64	15.0	26.8	4.6	11.3	17.9	5.5
65-74	29.4	43.8	17.8	16.0	21.9	11.1
≥75	38.5	53.8	23.1	19.2	30.8	7.7
≥18	6.8	10.8	3.4	8.7	11.4	6.3
≥45	13.5	22.2	6.3	10.7	15.2	6.9
≥55	20.0	32.6	9.1	13.1	19.9	7.2
≥65	30.7	45.3	18.4	16.4	23.3	10.7

10.8%; women 3.4%) by using fixed ratio criterion, respectively.

For the subjects aged 45 or more, the numbers of the subjects with airflow limitation were 117 for LLN criterion and 148 for fixed ratio criterion. So the crude prevalence rate of airflow limitation was 10.7% by LLN criterion and 13.5% by fixed ratio criterion in that population. The crude prevalence rates of airflow limitation increased as the age of population increased (Table 4). The prevalence rate by LLN and fixed ratio in age ≥ 65 was 16.4% and 30.7%, respectively.

Prevalence rate of COPD among the subjects aged 45 or older

The age adjusted standardized prevalence rates of COPD were 10.9% (men, 14.7%; women, 7.2%) by LLN criterion and 15.5% (men, 21.8%; women, 9.1%) by fixed ratio criterion. This rate also increased as the age of population in-

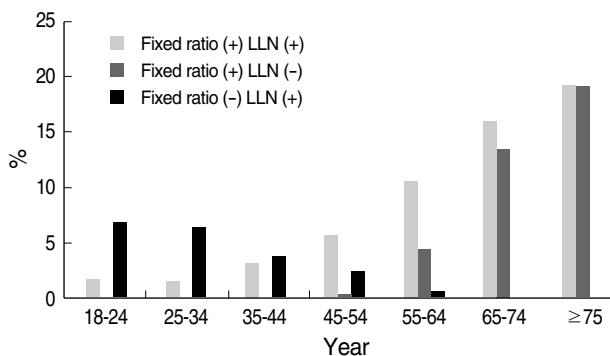


Fig. 1. Comparison of the number of subjects with airflow limitation of all age groups.

Fixed ratio (+), observed $FEV_1/FVC < 0.7$; LLN (+), observed $FEV_1/FVC < LLN$.

creased. The prevalence rate of COPD by LLN and fixed ratio in age ≥ 65 was 14.9% and 31.1%, respectively.

Comparison of the presence of airflow limitation by LLN and fixed ratio

We made a table for different age groups to evaluate the concordance of the each criterion for the presence of airflow limitation. The discrepancy rates were around 5% in each age group.

There were total 146 subjects who were differently classified according to the each criterion, 100 were classified as having airflow limitation by LLN criterion but not having airflow limitation by fixed ratio criterion. The remaining 46 were classified as having airflow limitation by fixed ratio criterion but not having airflow limitation by LLN criterion.

For subjects aged less than 45 yr, 38 subjects had airflow limitation by both fixed ratio criterion and LLN criterion. For subjects of age 65 or older, among the 31 subjects with airflow limitation by the LLN criterion, no one classified as without airflow limitation by the fixed ratio criterion. On the contrary, 27 subjects with airflow limitation by fixed ratio criterion did not show airflow limitation by LLN criterion.

Fig. 1 shows the proportion of subject with airflow limitation using both criteria in each age group. The percentage of subjects with airflow limitation by LLN criterion only decreased as the subjects' age increased. On the contrary, the percentage of subjects with airflow limitation by fixed ratio alone increased as the subjects' age increased. Among subjects older than 75 yr of age, half of the subjects with airflow limitation by fixed ratio criterion did not show airflow limitation by LLN criterion.

DISCUSSION

We analyzed 2,728 subjects who met new spirometry criteria for acceptability and repeatability from Korean nation-

al COPD survey. The age adjusted prevalence rate of COPD in the general population of Korea varies, according to the criterion used for its definition, from 10.9% with LLN criterion to 15.5% with fixed ratio criterion.

The ATS/ERS recently revised their spirometry recommendations, which included changes in spirometry acceptability and repeatability criteria (15). As the Korean NHANES II used the previous the ATS spirometry recommendations (16), we did not use the prediction equation that derived from Korean NHANES II (14). Instead, we made a new prediction equation for FEV_1/FVC . The mean differences between the predictive values of our new equation and other equations including the equation from the Korean NHANES II (14, 18-21) were about 1%, therefore it was reasonable to use our new equation.

There were 146 subjects who were differently classified according to each criterion. The discrepancy rate was 5.35% of the study population. This discrepancy rate was greater in older age groups and more prominent as age increased. And, there was different pattern of discrepancy according to age groups. For the younger subjects, more subjects were classified with airflow limitation by the LLN criterion. Contrarily, more subjects were classified with airflow limitation by fixed ratio criterion for the older subjects. These results implied that use of LLN may reduce the prevalence of COPD in elderly.

We previously reported 17.2% of the prevalence rate of COPD from the same nationwide COPD survey. But our previous study was performed based on the 1991 ATS spirometry recommendations and analyzed subjective who underwent at least two spirometry measurements acceptable by the 1991 ATS criteria (11). Our present study reselected study population according to the new ATS/ERS spirometry recommendations for the acceptability and repeatability (15). The crude prevalence rate of airflow limitation in the present study was lower than that of our previous study in subjects aged 45 or more. The prevalence rate of COPD by the fixed ratio criterion of the present study was 15.5%, which was lower than previous results (11). This meant that use of more strict criteria for spirometry also may reduce the prevalence rate of COPD in the elderly.

Since there had been no consensus on the criteria for diagnosis of COPD recently, a majority of national guidelines had their own diagnostic criteria of COPD (6-9, 23). The prevalence rate of COPD population depends on the criterion for the definition of airflow limitation even in the same population (24). After the GOLD guideline was introduced in 2001, a consensus of the diagnostic criterion of COPD was made; $FEV_1/FVC < 0.7$ (1, 11). But the definition of an obstructive pulmonary defect given in the recently published ATS/ERS spirometry recommendations contrasts with the definition suggested by the GOLD and ATS/ERS guidelines, in that FEV_1 is referred to vital capacity (VC) rather than just FVC and the cut-off value of this ratio is set at the 5th percentile

of the normal distribution rather than at a fixed ratio of 0.7. The advantage of using VC in place of FVC is that the ratio of FEV₁ to VC is capable of accurately identifying more obstructive patterns than its ratio to FVC, because FVC is more dependent on flow and volume histories (13).

There were few studies comparing the lower limit of normal (LLN) to fixed ratio for the detection of airflow limitation to diagnose COPD. Our present study showed that use of LLN criterion for the diagnosis of COPD decreased the prevalence rate as much as 4.6% for the subject with aged ≥ 45 yr. This result corresponds with the earlier study by Celli et al., which evaluated the impact of five different definitions of airflow limitation on the estimated prevalence of COPD (17). Our study also showed that 27 subjects (14.3%) with airflow limitation by fixed ratio criterion did not show airflow limitation by LLN criterion for subjects of age 65 or older. This figure was comparable to that of recent study by Hansen et al. which reported that using fixed ratio criterion misidentified 11.3% of subject of age seventh and eighth decade as abnormal (25). But in contrary to our study, both studies used the 1994 ATS spirometry recommendations. We believe this study to be the only one which adopted new 2005 ATS/ERS spirometry recommendations to date.

This study has some limitations though. The spirometric definitions of COPD generally require post-bronchodilator measurement (1, 10), but the spirometry examination in this nationwide survey did not include a test of reversibility of obstruction. While some subset of the study population had probability of having pure asthma, we believe the prevalence figure of airflow limitation is reasonable as a criterion of the prevalence of COPD especially after the age of 45 yr in this large epidemiologic survey. We understand that the reference equations using post-bronchodilator measurement of lung parameter are not validated (1, 26). The other limitation is that we did not use the LLN of the vital capacity (VC) recommended by the ATS/ERS to differentiate the pure obstructive defect from the mixed defect (13). The FVC is usually reduced more than IVC (inspiratory vital capacity) or SVC (slow vital capacity) in airflow obstruction (27). However, the effect of these differences on population estimates has not been studied (17). So the ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) seemed to be reasonable indicator of the presence of the airflow limitation in this large epidemiologic survey.

Our study found that 10.9% of Korean adults over the age of 45 yr had COPD by LLN criterion, which reduced the prevalence rate of COPD by 4.6% point. More strict application of spirometry criteria for acceptability and repeatability also reduced the prevalence of COPD.

In conclusion, adopting LLN and more strict spirometry criteria revealed lower prevalence rate of COPD in elderly Korean population. Particularly, using LLN criterion might reduce the risk of over-diagnosis of COPD in the elderly.

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