



Strategies for Management of the Early Chronic Obstructive Lung Disease

Jung Yeon Lee, M.D.¹, Chin Kook Rhee, M.D., Ph.D.², Ki Suck Jung, M.D., Ph.D.³ and Kwang Ha Yoo, M.D., Ph.D.⁴

¹Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Konkuk University Chungju Hospital, Chungju, ²Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, ³Division of Pulmonary Medicine, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, ⁴Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea

Lung function reportedly declines with age and that this decline is accelerated during disease progression. However, a recent study showed that the decline might peak in the mild and moderate stage. The prognosis of chronic obstructive pulmonary disease (COPD) can be improved if the disease is diagnosed in its early stages, prior to the peak of decline in lung function. This article reviews recent studies on early COPD and the possibility of applying the U.S. Preventive Services Task Force recommendation 2008 and 2015 for early detection of COPD in Korea.

Keywords: Pulmonary Disease, Chronic Obstructive; Early Diagnosis; Guideline; Recommendations, Health Planning

Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) in persons aged >40 years was 13.4% based on the 2008 Korea National Health and Nutrition Examination Survey (KNHANES), and approximately 94% of the cases were classified as mild and moderate COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document¹. Most of these cases were not diagnosed and/or treated as COPD. Indeed, subjects with early COPD

have minor or no symptoms at all. However, their pathophysiological conditions and socioeconomic burdens are known to be similar to those of subjects with more-severe COPD. For this reason, reducing the disease burden is important by detection of subjects with early COPD and treatment with drugs combined with behavioral treatment such as smoking cessation, education, and air pollution control, which also can prevent disease progression. However, studies that investigate whether detection and treatment of early COPD lessen the disease burden are rare. This statement is based on a recent literature review conducted for evaluation of the effectiveness of detection, research, and treatment of early COPD.

Address for correspondence: Kwang Ha Yoo, M.D., Ph.D.

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Konkuk University School of Medicine, 120 Neungdong-ro, Gwangjin-gu, Seoul 05029, Korea

Phone: 82-2-2030-7522, **Fax:** 82-2-2030-7748

E-mail: khyou@kuh.ac.kr

Received: Dec. 9, 2015

Revised: Dec. 24, 2015

Accepted: Jan. 6, 2016

© It is identical to the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>).



Copyright © 2016
The Korean Academy of Tuberculosis and Respiratory Diseases.
All rights reserved.

Definition of Early COPD in Terms of Severity

Early COPD has not been defined clearly because of the variability of airflow within and across a population, and the reduction of lung volume with age^{2,3}. However, most often, postbronchodilation 1 second forced expiratory volume (FEV₁)-to-forced vital capacity (FVC) ratio ≤ 0.7 and FEV₁ >50% of the predicted normal value were used in spirometry regardless of respiratory symptoms⁴. In South Korea, substantial agreement on the definition of early COPD has not been reached yet. However, suggestion have been made by using

the spirometric criteria ($FEV_1/FVC \leq 0.7$ and $FEV_1 > 60\%$ of the normal predicted value) according to the Korean COPD Guideline, considering criteria of the group “ga,” “na,” and “da” and using the term “very early COPD” rather than “early COPD” to avoid confusion with foreign reports.

Early-Onset COPD

Early-onset COPD is sometimes interpreted as COPD occurring at an early age. Generally, COPD has been known to occur in persons older than 40 years and adult smokers. However, considering subjects who do not visit physicians and the individual variability of lung function, it is not entirely impossible to develop COPD at a young adult age. It is interesting that compared with healthy people, these patients are characterized by low peak lung function in their twenties. A common cause of low peak lung function is childhood asthma⁵ and maternal smoking during pregnancy⁶. The National Heart, Lung, and Blood Institute reports that 12 million Americans have COPD and that another 12 million Americans are estimated to have the disease without knowing it⁷. According to the report of a pre-specified *post hoc* analysis of 356 patients aged ≤ 50 years who had COPD and enrolled in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study, the number of women in the ≤ 50 year age group was higher but disease severity as classified based on GOLD stage was similar to that in the total population. About half of the subjects in the ≤ 50 -year-old cohort continued to smoke, whereas the percentage of continuing smokers progressively decreased with age⁸. Despite the similar objective indexes of disease severity, health-related quality of life was substantially poorer in the patients aged < 50 years⁸. In another study by Sanchez-Salcedo et al.⁹, the disease severity distribution and progression (lung function decline) in younger patients with COPD were similar to those in older patients⁹. Hence, the response of young patients with COPD to pulmonary rehabilitation was similar to that of old patients¹⁰.

Importance of Early COPD

In South Korea, the KNHANES performed spirometry in all subjects aged > 40 years and found that the incidence of COPD was 13.4% in a 2008 study¹¹. Among the patients, about 94% had mild-to-moderate COPD (early COPD) according to the GOLD staging system, with little or without apparent symptoms¹¹. In the 2008 KNHANES report, only 2.4% (9/353) of subjects were diagnosed by a physician and only 2.1% (8/353) underwent treatment¹. This means that although the prevalence of COPD in Korea is high, most of the cases were underdiagnosed and undertreated. Another study in the United States, which was conducted during the period from 2007

through 2010 by the National Health and Nutrition Examination Survey (NHANES), also suggested that the overall age-adjusted prevalence of any obstructive lung disease was 13.5% and reported that 50% of cases were early COPD¹².

Owing to the rare symptoms and relatively favorable pulmonary function, subjects with early COPD have the tendency to not visit a hospital. In primary health-care institutions in Korea, spirometry, which is the most important diagnostic study for COPD, has not been performed effectively. Hence, subjects with early COPD could lose the opportunity undergo diagnosis and treatment before disease manifestation. Even subjects with early COPD are known to have pathological changes¹³, and more-severe systemic inflammation¹⁴ and more comorbidities than healthy subjects with conditions compatible with established COPD¹⁵.

According to the basic data investigation for the medical cost of treatment of early COPD ($FEV_1 > 50\%$ of the predictive value), the 2012 domestic study reported that each subject spent Korean won (KRW) 890,000 per year (*Policy Development Research Work Report of The Development of Strategies for the Prevention and Control of COPD*⁷), showing a high medical care expenditure.

In addition, patients with early COPD have been known to experience acute exacerbation. In registered subjects in well-known cohorts such as those of the TORCH, UPLIFT, and ECLIPSE studies, those who met the criteria of $FEV_1/FVC \leq 0.7$ and $FEV_1 > 50\%$ of the predicted normal value were reported to have acute exacerbation at a maximum of 0.9 time, roughly 1 time per year¹⁶. Traditionally, lung function decline in patients with COPD has been known to be accelerated as the disease progresses over time¹⁷. However, a recent paper showed that the annual decline of pulmonary function was more severe in patients with early COPD than in those with severe to very severe COPD¹⁸. Therefore, early detection and active treatment before lung function decline, that is, progression to a more severe status, is important for reducing acute exacerbation, which improves quality of life, and decreases medical expenditure and mortality.

Even with their minor symptoms, subjects with early COPD have the same level of socioeconomic burden as those with severe COPD, but studies that investigate, for example, treatment effectiveness among these subjects are rare. The overseas representative cohort of patients with COPD is limited to those with the most severe cases in the ECLIPSE and COPD gene research. Research about early COPD is limited. In particular, early COPD is registered in relation to the concept of control of progression to severe COPD. This is perhaps because patients with early COPD have no or mild symptoms and do not visit hospitals, making enrollment more difficult than that of patients with severe symptoms. Determining the effectiveness of treatment of severe COPD could be more useful. Recently, however, reports indicated the benefit of early treatment to patients with early COPD in terms of disease process, in compar-

ison with no treatment. Patients who underwent appropriate treatment of early COPD had improved lung function¹⁹ and reduced acute exacerbation²⁰; thereby, their medical expense was reduced²¹. In addition, the rates of lung function and mortality were more significantly reduced in patients with mild to moderate COPD who stopped smoking than in those who continued smoking^{22,23}. Subjects with early COPD who underwent respiratory rehabilitation had fewer hospital admissions and less medical costs²⁴ and had better exercise capacity than the control group²⁵. Even though none of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function, the GOLD document recommends that influenza and pneumococcal vaccinations should be offered depending on local guidelines³. Moreover, all COPD patients benefit from exercise training programs, showing improvements in exercise tolerance and symptoms of dyspnea and fatigue³. Overall, aggressive treatment should be considered for patients with early COPD.

Early COPD could be identified in two groups based on the COPD GOLD or Korean domestic guidelines^{16,26}. The two groups included subjects with slight deterioration in lung function ($FEV_1 >50\%$ of the predicted normal value) with fewer symptoms¹⁶ (or $FEV_1 >60\%$ of the predicted normal value, GOLD A, group “ga”²⁶) and those with slight deterioration in lung function with more symptoms (GOLD B, group “na”), respectively. Although no immediate large-scale study has been conducted, screening is expected to provide beneficial results to patients, considering the above-mentioned reports. However, the 2008 U.S. Preventive Services Task Force (USPSTF) recommended against screening adults for COPD by using spirometry (USPSTF recommendation state grade D)¹⁸. For example, under the best-case assumptions about response to therapy, an estimated 455 adults between 60 and 69 years of age would need to be screened to defer one exacerbation²⁷. Thus, taking into account the cost and effectiveness of screening, they suggest that diagnostic tests not be performed in patients without symptoms. However, the USPSTF recommendations were relatively old by the 2008 report. Since then, several recent studies have been reported about the pathophysiological mechanism and treatment of COPD, and the updated 2015 USPSTF was also released. Based on the recent literature, whether screening should be performed as the USPSTF recommended or not should be reconsidered because of the relatively higher prevalence of early COPD in Korea than in the United States, where lung function tests are low-cost.

U.S. Preventive Services Task Force Recommendation 2008 and 2015

1. The benefits of screening and smoking cessation

The 2008 USPSTF described that all individuals with COPD,

including those with mild or moderate illness, would benefit from smoking cessation. However, fair evidence shows that providing smokers with spirometry results does not independently improve cessation rates. Thus, spirometric screening is not necessary for asymptomatic subjects²⁷. However, one study showed that smoking cessation rates more than doubled when lung function tests were performed and spirometric test results with lung age were released for 561 smokers aged >35 years ($p=0.01$)^{28,29}. That is, providing subjects with spirometric test results with lung age and lung function test results might be effective for increasing smoking cessation rates. After that study, no trials were found that directly assessed if screening asymptomatic adults aged >40 years for COPD is useful in terms of improving health-related quality of life or reducing morbidity or mortality²⁹. However, the 2015 USPSTF showed that in high-risk asymptomatic adults, screening for COPD using prescreening questionnaires such as the COPD diagnostic questionnaire, focusing mainly on primary care population, detected mild or moderate disease in most of the patients (83.8% to 94.7%)^{30,31}.

2. Benefits of early treatment

In the 2008 USPSTF, good evidence suggests that pharmacological therapy prevents exacerbations (worsening of symptoms and the need for medical care) but does not affect hospitalizations or all-cause mortality among symptomatic individuals who have been smokers in the past (“ever smokers”) who are 40 years or older.

Since then, large-scale updated studies have been conducted. A *post hoc* analysis in a study that targeted 2,156 subjects with $FEV_1 >50\%$ of the predicted normal value in the TORCH trial, which aimed to determine the effective treatment for decreasing mortality rate in COPD, suggested that drug management showed reduced mortality rate and number of acute exacerbations ($p<0.05$)²⁰. The *post hoc* analysis of 2,739 subjects with early COPD in the UPLIFT study also showed that treatment of COPD with inhaler reduced the annual decline of lung function and the number of hospitalizations owing to acute exacerbation of approximately 20%³². Cases with $FEV_1 >60\%$ also showed decreased mortality and acute exacerbation³³. The 2015 USPSTF stated that they identified no trials that addressed the effectiveness of any treatment to improve health outcomes in patients with mild COPD. Nonetheless, even relatively weak data consistently support some reduction in exacerbations for each of the treatment classes, especially long acting beta-2 agonist (LABA) and tiotropium, in subjects with mild to moderate COPD. To sum up, recent large-scale studies suggested that symptomatic GOLD B group “na” subjects benefitted from medication.

3. The harms of detection and early treatment

In the 2008 USPSTF, fair evidence indicates that spirometry can lead to substantial over diagnosis of COPD in “never smokers” aged >70 years. Even though a comparison study was conducted to compare effectiveness between using a fixed ratio and using the lower limit of normal (LLN) for diagnosing COPD, no study has compared the two groups of subjects. Generally, using the LLN could reduce the prevalence of COPD, which means that the high-risk group who need hospitalization could be excluded. Thus, further research is needed to target multiple-risk groups. However, compared with using a fixed ratio, using the LLN for diagnosing COPD reduces the risk of over diagnosis³⁴. The 2015 USPSTF found no evidence to estimate the long-term harms of these screening tests. The potential harms of treatment may include pneumonia with the use of LABA and inhaled corticosteroids, and decreased bone density and increased fractures with the use of inhaled corticosteroids. However, data were sparse, with few adverse events, and no differences were found between the intervention and control groups³. For all classes of medications, the one consistent finding was that treatment suppressed COPD exacerbation in persons with moderate COPD, without consistent effects on all-cause mortality, dyspnea, or quality of life and evidence on the effects of treatment on exercise capacity was insufficient. As all of the treatment trials were conducted in persons with mild to moderate COPD, how these results would apply to asymptomatic populations is unclear. Given the lack of potential benefits of treatment in asymptomatic persons and the non-trivial efforts of screening, the USPSTF determined that there is no net benefit of screening.

4. Cost effectiveness for screening of COPD

The 2008 USPSTF stated that the opportunity costs associated with screening for COPD using spirometry are high even in populations at higher risk. This means that its cost effectiveness is low. Recent guidelines from the GOLD 2015 recommend case finding in symptomatic patients but not screening in asymptomatic populations³.

However, in the tertiary US NHANES, the prevalence of COPD was 2.6% in subjects aged >50 years³⁵. Korea showed a relatively higher prevalence (9.0% in women and 15.0% in men)¹. In addition, the cost for lung function test using a bronchodilator in the United States was \$100 or higher, but around \$25 in Korea, which means that it is highly cost-effective in the domestic situation than in the United States. Whether early detection of COPD, education, and care are needed for subjects who do not recognize or report their symptoms should be studied at a national level. And health screening might be revised to include active lung function tests in order to detect early COPD.

Conclusion

Whereas the prevalence of early COPD is higher than that of severe or very severe COPD, the tendency of subjects to visit hospital is low. Taking into account the many recent studies, the benefit of treatment for group B or the Korean group “na,” who had more complaints of symptoms with fair lung function, is thought to be considerably high. The GOLD document and domestic Korean guideline suggested active treatment for this group of patients. In reality, patients with early COPD with mild symptoms visit primary clinics first. Thus, a simple test method should be developed for effectively diagnosing early COPD in primary clinics. It is relatively difficult to implement the lung function test in primary healthcare clinics because of the need for medical technicians to conduct the lung function test and the difficulties of quality control. Currently, the Health Insurance Review and Assessment Service has implemented the COPD adequacy assessment. Considering the lung function test implementation rate contained in the evaluation of adequacy items, a simple test method needs to be developed for use in primary clinics, combined with research to evaluate the effectiveness and usefulness of the test. On the other hand, due to the relatively higher actual medical cost in the United States than in Korea for the detection of early COPD patients in GOLD A or group “ga,” research studies are needed to verify the effectiveness of early diagnosis and intervention. Then, we can contemplate on a number of studies published in the last decades. Even though USPSTF 2015 recommendation again came out, there were no significant changes and the recommendation strength was D. So, the USPSTF 2008 and 2015 recommendation should be modified according to the current situation in Korea. As studies regarding early COPD are few, research for these patients is needed. Conducting studies regarding clinical characteristics, risk factors, and prognosis is top priority. Furthermore, clinical trials regarding treatment response to inhalers in early COPD patients are also needed. Whether early treatment of early COPD is effective should be validated in terms of not only clinical parameters but also economic parameters.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Yoo KH, Kim YS, Sheen SS, Park JH, Hwang YI, Kim SH, et al. Prevalence of chronic obstructive pulmonary disease in Korea: the fourth Korean National Health and Nutrition Examination Survey, 2008. *Respirology* 2011;16:659-65.

2. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008;63:1046-51.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for diagnosis, management and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease; 2007.
4. Decramer M, Miravittles M, Price D, Roman-Rodriguez M, Llor C, Welte T, et al. New horizons in early stage COPD: improving knowledge, detection and treatment. *Respir Med* 2011;105:1576-87.
5. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax* 2014;69:805-10.
6. Bateman ED, Reddel HK, van Zyl-Smit RN, Agusti A. The asthma-COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? *Lancet Respir Med* 2015;3:719-28.
7. Centers for Disease Control and Prevention. Policy Development Research Work Report. The development of strategies for the prevention and control of COPD. Atlanta: Centers for Disease Control and Prevention; 2013.
8. Morice AH, Celli B, Kesten S, Lystig T, Tashkin D, Decramer M. COPD in young patients: a pre-specified analysis of the four-year trial of tiotropium (UPLIFT). *Respir Med* 2010;104:1659-67.
9. Sanchez-Salcedo P, Divo M, Casanova C, Pinto-Plata V, de-Torres JP, Cote C, et al. Disease progression in young patients with COPD: rethinking the Fletcher and Peto model. *Eur Respir J* 2014;44:324-31.
10. Katsura H, Kanemaru A, Yamada K, Motegi T, Wakabayashi R, Kida K. Long-term effectiveness of an inpatient pulmonary rehabilitation program for elderly COPD patients: comparison between young-elderly and old-elderly groups. *Respirology* 2004;9:230-6.
11. Hwang YI, Kim CH, Kang HR, Shin T, Park SM, Jang SH, et al. Comparison of the prevalence of chronic obstructive pulmonary disease diagnosed by lower limit of normal and fixed ratio criteria. *J Korean Med Sci* 2009;24:621-6.
12. Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the National Health and Nutrition Examination surveys from 1988-1994 to 2007-2010. *Chest* 2013;143:1395-406.
13. Rodriguez-Roisin R, Drakulovic M, Rodriguez DA, Roca J, Barbera JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. *J Appl Physiol* (1985) 2009;106:1902-8.
14. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012;7:e37483.
15. Van Remoortel H, Hornikx M, Langer D, Burtin C, Everaerts S, Verhamme P, et al. Risk factors and comorbidities in the pre-clinical stages of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014;189:30-8.
16. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease; 2011.
17. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;1:1645-8.
18. Tantucci C, Modina D. Lung function decline in COPD. *Int J Chron Obstruct Pulmon Dis* 2012;7:95-9.
19. Johansson G, Lindberg A, Romberg K, Nordstrom L, Gerken F, Roquet A. Bronchodilator efficacy of tiotropium in patients with mild to moderate COPD. *Prim Care Respir J* 2008;17:169-75.
20. Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respir Res* 2009;10:59.
21. van den Boom G, Rutten-van Molken MP, Molema J, Tirimanna PR, van Weel C, van Schayck CP. The cost effectiveness of early treatment with fluticasone propionate 250 microg twice a day in subjects with obstructive airway disease. Results of the DIMCA program. *Am J Respir Crit Care Med* 2001;164:2057-66.
22. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994;272:1497-505.
23. Pelkonen M, Tukiainen H, Tervahauta M, Notkola IL, Kivela SL, Salorinne Y, et al. Pulmonary function, smoking cessation and 30 year mortality in middle aged Finnish men. *Thorax* 2000;55:746-50.
24. Golmohammadi K, Jacobs P, Sin DD. Economic evaluation of a community-based pulmonary rehabilitation program for chronic obstructive pulmonary disease. *Lung* 2004;182:187-96.
25. Riario-Sforza GG, Incorvaia C, Paterniti F, Pessina L, Caligiuri R, Pravettoni C, et al. Effects of pulmonary rehabilitation on exercise capacity in patients with COPD: a number needed to treat study. *Int J Chron Obstruct Pulmon Dis* 2009;4:315-9.
26. The Korea Academy of Tuberculosis and Respiratory Diseases; COPD Guideline Revision Committee. The COPD guideline in Korea: update in 2014. Seoul: The Korean Academy of Tuberculosis and Respiratory Diseases; 2014.
27. U.S. Preventive Services Task Force. Screening for chronic obstructive pulmonary disease using spirometry: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;148:529-34.
28. Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking

- quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *BMJ* 2008;336:598-600.
29. Guirguis-Blake JM, Senger CA, Webber EM, Mularski R, Whitlock EP. Screening for chronic obstructive pulmonary disease: a systematic evidence review for the U.S. Preventive Services Task Force. Rockville: Agency for Healthcare Research and Quality; 2015.
 30. Sichletidis L, Spyrtatos D, Papaioannou M, Chloros D, Tsiotsios A, Tsagaraki V, et al. A combination of the IPAG questionnaire and PiKo-6(R) flow meter is a valuable screening tool for COPD in the primary care setting. *Prim Care Respir J* 2011;20:184-9.
 31. Frith P, Crockett A, Beilby J, Marshall D, Attewell R, Ratnanesan A, et al. Simplified COPD screening: validation of the PiKo-6(R) in primary care. *Prim Care Respir J* 2011;20:190-8.
 32. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP, et al. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009;374:1171-8.
 33. Tashkin DP, Celli BR, Decramer M, Lystig T, Liu D, Kesten S. Efficacy of tiotropium in COPD patients with FEV1 \geq 60% participating in the UPLIFT(R) trial. *COPD* 2012;9:289-96.
 34. van Dijk WD, Gupta N, Tan WC, Bourbeau J. Clinical relevance of diagnosing COPD by fixed ratio or lower limit of normal: a systematic review. *COPD* 2014;11:113-20.
 35. Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med* 2000;160:1683-9.