Clinical Relevance of Fixed Ratio vs Lower Limit of Normal of FEV₁/FVC in COPD: Patient-Reported Outcomes From the CanCOLD Cohort

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ABSTRACT

PURPOSE The way in which spirometry is interpreted can lead to misdiagnosis of chronic obstructive pulmonary disease (COPD) resulting in inappropriate treatment. We compared the clinical relevance of 2 criteria for defining a low ratio of forced expiratory volume in 1 second to forced vital capacity (FEV₁/FVC): the fixed ratio and the lower limit of normal.

METHODS We analyzed data from the cross-sectional phase of the population-based Canadian Cohort of Obstructive Lung Disease (CanCOLD) study. We determined associations of the spirometric criteria for airflow limitation with patient-reported adverse outcomes, including respiratory symptoms, disability, health status, exacerbations, and cardiovascular disease. Sensitivity analyses were used to explore the impact of age and severity of airflow limitation on these associations.

RESULTS We analyzed data from 4,882 patients aged 40 years and older. The prevalence of airflow limitation was 17% by fixed ratio and 11% by lower limit of normal. Patients classified as having airflow limitation by fixed ratio only had generally small, nonsignificant increases in the odds of adverse outcomes. Patients having airflow limitation based on both fixed ratio and lower limit of normal had larger, significant increases in odds. But strongest associations were seen for patients who had airflow limitation by both fixed ratio and lower limit of normal and also had a low FEV₁, defined as one less than 80% of the predicted value.

CONCLUSIONS Our results suggest that use of the fixed ratio alone may lead to misdiagnosis of COPD. A diagnosis established by both a low FEV₁/FVC (according to fixed ratio and/or lower limit of normal) and a low FEV₁ is strongly associated with clinical outcomes. Guidelines should be reconsidered to require both spirometry abnormalities so as to reduce overdiagnosis of COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent chronic diseases and the cause of much morbidity and mortality worldwide.¹ COPD has been estimated to occur in up to 25% of the population aged 40 years and older¹,²; however, both overdiagnosis and underdiagnosis pose challenges in daily practice, resulting in inappropriate patient management.²-¹⁰ COPD guidelines recommend the use of a low ratio of forced expiratory volume in 1 second to forced vital capacity (FEV₁/FVC) to establish the diagnosis in patients with chronic respiratory symptoms or those at risk.¹,¹¹,¹²

There is currently no consensus on the best criteria to be used for the spirometric confirmation of a clinical diagnosis of COPD. A lively debate revolves around 2 main measures. One measure is the FEV₁/FVC fixed ratio of less than 0.7, alone or in combination with a low FEV₁ set at a value less than 80% of predicted; the combination comprises Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 or worse disease. The other measure is the FEV₁/FVC ratio below the 5th percentile, in other

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words, below the lower limit of normal (LLN).\textsuperscript{1,11-17} Prevalence studies have shown discordance between the fixed ratio and LLN, suggesting potential overdiagnosis by the former or underdiagnosis by the latter.\textsuperscript{3,4,8,18,19}

This controversy persists because of the absence of a reference standard for the diagnosis of COPD.\textsuperscript{19} The associations of the 2 criteria with clinical outcomes have been assessed in a few studies, with unclear results on the relative superiority of 1 criterion over the other when it comes to their relationship with different clinical outcomes.\textsuperscript{20} The cross-sectional phase of the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study provided us with a large population-based database to further explore the clinical relevance of these criteria by examining their associations with multiple patient-reported outcomes such as symptoms, health status, dyspnea-related disability, exacerbations, and cardiovascular comorbidity, with adjustments for age, sex, and smoking exposure.

METHODS

We analyzed data from 5,176 people from the general population aged 40 years and older to assess the clinical relevance of differing diagnostic criteria for COPD. Data were collected between August 2005 and May 2009 in a large, cross-sectional, multisite, population-based study on lung health, which constituted the first phase of the longitudinal CanCOLD study. The sampling strategy and study protocol of the baseline cross-sectional part of the study were the same as those used in the international Burden of Obstructive Lung Disease (BOLD) initiative, the full details of which have been published elsewhere.\textsuperscript{21} Briefly, random samples of noninstitutionalized adults from 9 Canadian urban sites were drawn from census data of Statistics Canada (Survey and Analysis Section), and recruitment was conducted by the NRG Research group by random telephone digit dialing to identify eligible individuals\textsuperscript{21} who were invited to attend a clinic visit to complete interviewer-administered respiratory questionnaires and to perform pre- and post-bronchodilator spirometry. The only exclusion criterion was inability or refusal to perform spirometry. The mean clinic visit participation rate was 74\% (range, 63\% to 87\%).\textsuperscript{21} All participants gave written informed consent, and the study was approved by the respective institutional ethical review boards. CanCOLD is registered at http://www.clinicaltrials.gov (NCT00920348).

Measurements

Spirometry was performed according to the acceptability and reproducibility criteria of the American Thoracic Society and European Respiratory Society guidelines.\textsuperscript{22} Measurements included FEV\textsubscript{1} and FVC. Data in administered questionnaires provided information on age, sex, body mass index, educational level, and race; smoking status, including number of pack-years; and the patient report of physician-diagnosed COPD, emphysema, and chronic bronchitis.

Additional questionnaire data included patient-reported outcomes: (1) respiratory symptoms including chronic cough and chronic phlegm for most days during 3 months in the last year; chronic bronchitis (defined as chronic cough and chronic phlegm for more than 2 years); and wheeze in the last year (not only during colds); (2) disability by the Medical Research Council (MRC) dyspnea scale; (3) general health status as assessed by the Short Form 12-item health survey (SF-12); (4) self-reported exacerbations of COPD; and (5) self-reported physician-diagnosed cardiovascular disease.

We compared 2 spirometric criteria for determining airflow limitation—a postbronchodilator FEV\textsubscript{1}/FVC ratio of less than 0.70 (fixed ratio) and a postbronchodilator FEV\textsubscript{1}/FVC ratio of less than the 5th percentile (LLN)—using the reference equations from the Third National Health and Nutrition Examination Survey (NHANES III).\textsuperscript{23} We assessed diagnosis according to presence of either or both criteria.

Outcomes and Modifying Factors

We defined clinically relevant outcomes as follows: respiratory symptoms including chronic cough, chronic phlegm, chronic bronchitis, and wheeze; health status, as measured by SF-12; disability, as measured by MRC dyspnea scale; exacerbations of COPD as measured by ever having breathing problems that interfered with usual daily activities or caused one to miss work; and cardiovascular disease (heart disease and stroke).

We assessed a variety of factors for their potential modification of the relationship between the 2 diagnostic criteria and clinically relevant outcomes, including sex, age-group (younger or older than 60 years), cardiovascular disease, and smoking status. In particular, we studied the impact of the severity of airflow limitation, assessed by FEV\textsubscript{1}, as the percentage of the predicted value, on the association of fixed ratio or LLN with the outcomes.

Statistical Analysis

We analyzed the associations of the 2 main diagnostic criteria with clinically relevant outcomes. In addition, we compared 6 subgroups of individuals who satisfied various diagnostic criteria consisting of single spirometric measures or combinations of measures. Univariate analysis of variance (ANOVA) and the Kruskal-Wallis test for continuous variables,
and the χ² square test for dichotomous variables were performed to compare the subgroups on baseline characteristics. We analyzed the clinical relevance of the diagnostic criteria according to the subgroups by a multivariate regression model, controlling for confounders at baseline. Logistic models were used for binary data, and linear models were used for continuous data. In addition, we performed interaction analyses between the spirometric criteria and modifying factors to determine whether any of these factors significantly modified the association with clinical outcomes. Finally, sensitivity analyses were performed by including 2 additional subgroups with a low FEV₁, defined as a value less than 80% of predicted: a subgroup meeting the fixed ratio criterion and having low FEV₁ (ie, GOLD stage 2 or higher disease) and subgroup meeting the LLN criterion and having low FEV₁.

A P value of less than .05 was considered to be statistically significant.

RESULTS

Analyses were based on 4,882 CanCOLD study participants who had complete data on all study parameters (Table 1). Their mean age (±SD) was 57 (±11) years, with a range of 40 to 93 years; 146 (3%) were older than 80 years. Forty-three percent were male. Their mean FEV₁ (±SD) was 95.0% (±17%) of the normal predicted value.

The prevalence of spirometric airflow limitation

| Characteristic                        | Total (N = 4,882) | No Airflow Limitation (n = 4,038) | Airflow Limitation |               |               |
|---------------------------------------|-------------------|----------------------------------|--------------------|---------------|---------------|
|                                       |                   |                                  | FR+/LLN= (n = 297) | FR-/LLN+ (n = 15) | FR+/LLN+ (n = 532) | FR+ and Low FEV₁ (n = 363) | LLN+ and Low FEV₁ (n = 304) |
| Age, mean (SD), y                     | 57 (11)           | 56 (11)                          | 68 (10)            | 45 (3)        | 62 (12)       | 64 (11)           | 63 (11)               |
| Sex (male), No. (%)                   | 2,093 (43)        | 1,668 (41)                       | 186 (63)           | 1 (7)         | 238 (45)      | 177 (49)          | 138 (45)              |
| Postbronchodilator FEV₁, mean (SD), % predicted | 95 (17)           | 98 (15)                          | 92 (16)            | 77 (18)       | 77 (18)       | 65 (12)           | 64 (12)               |
| Postbronchodilator FVC, mean (SD), % predicted | 97 (15)           | 96 (15)                          | 101 (17)           | 99 (12)       | 98 (19)       | 85 (14)           | 86 (14)               |
| Body mass index, kg/m²                | 28 (6)            | 28 (6)                           | 27 (5)             | 28 (5)        | 28 (5)        | 28 (6)            | 28 (6)                |
| Tobacco smoking status, No. (%)       | 2,091 (43)        | 1,852 (46)                       | 95 (32)            | 8 (33)        | 136 (26)      | 73 (20)           | 100 (33)              |
|                                        | 2,058 (42)        | 1,657 (41)                       | 158 (53)           | 1 (7)         | 242 (46)      | 178 (49)          | 142 (47)              |
|                                        | 729 (15)          | 527 (13)                         | 43 (15)            | 6 (40)        | 153 (29)      | 111 (31)          | 61 (20)               |
|                                        | 493 (10)          | 366 (9)                          | 43 (15)            | 0 (0)         | 83 (16)       | 65 (18)           | 55 (18)               |
|                                        | 4,464 (91)        | 3,663 (91)                       | 277 (93)           | 14 (93)       | 510 (96)      | 343 (94)          | 290 (95)              |
| Conditions, No. (%)                   |                   |                                  |                    |               |               |                   |                       |
| Chronic cough                         | 619 (13)          | 432 (11)                         | 45 (15)            | 6 (40)        | 136 (26)      | 113 (31)          | 102 (34)              |
| Chronic phlegm                        | 467 (10)          | 312 (8)                          | 35 (12)            | 1 (7)         | 119 (22)      | 96 (26)           | 85 (28)               |
| Chronic bronchitis                     | 213 (4)           | 136 (3)                          | 17 (6)             | 1 (7)         | 59 (11)       | 51 (14)           | 65 (21)               |
| Wheeze                                | 1,273 (29)        | 939 (25)                         | 78 (31)            | 8 (33)        | 248 (52)      | 192 (60)          | 166 (61)              |
| MRC dyspnea scale¹                    | 1.4               | 1.3                              | 1.4                | 1.7           | 1.8           | 2                 | 2.03                  |
|                                       | (0.8)             | (0.7)                            | (0.8)              | (1.2)         | (1.1)         | (1)               | (1.2)                 |
| SF-12 scores, mean (SD)²              |                   |                                  |                    |               |               |                   |                       |
| Physical scale                        | 50 (9)            | 51 (9)                           | 50 (9)             | 46 (14)       | 47 (11)       | 45 (11)           | 44 (12)               |
| Mental scale                          | 52 (9)            | 52 (9)                           | 54 (8)             | 49 (11)       | 52 (9)        | 53 (9)            | 52 (10)               |
| Exacerbation, No. (%)                 | 996 (20)          | 779 (19)                         | 58 (20)            | 4 (27)        | 155 (29)      | 119 (33)          | 100 (33)              |
| Cardiovascular disease, No. (%)       | 605 (12)          | 436 (11)                         | 76 (26)            | 1 (7)         | 92 (17)       | 81 (22)           | 66 (22)               |

Notes: Continuous data are presented as mean (SD), dichotomous values as number (%). P value: univariate analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and χ² test for dichotomous variables.

1 FR-/LLN–.
2 FEV₁ <80% of predicted.
3 Collectively, these 2 criteria constitute Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 or higher disease.
4 Tobacco smoking status includes both cigarette and pipe smoking.
5 Chronic cough and chronic phlegm for more than 2 years.
6 MRC dyspnea scale scores range from 0 to 5; higher scores indicate worse health/dyspnea.
7 SF-12 Physical and Mental scale scores range from 0 to 100; higher scores indicate better health.
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was 17% by fixed ratio and 11% by lower limit of normal (Table 1). The majority of patients with airflow limitation satisfied both spirometric criteria as there was considerable overlap (concordance) between individuals meeting the fixed ratio and LLN cutoffs for diagnosis as shown in the Venn diagram depicting the proportions satisfying various criteria (Figure 1). The number of patients with airflow limitation by LLN but not by fixed ratio (discordance) was small, at just 15 (0.3%); these patients were on average younger and almost always female (Table 1). The prevalence of airflow limitation by fixed ratio was greater than that by LLN, except among young women; the greatest differences were seen among older adults (Figures 2 and 3).

Associations With Outcomes
Compared with peers who met neither criterion for airflow limitation, patients having airflow limitation based on fixed ratio only were significantly more likely to have physician-diagnosed wheeze (odds ratio [OR] = 1.54) and cardiovascular disease (OR = 1.52); associations with other outcomes showed only nonsignificant trends (Table 2). In contrast, patients who met both the fixed ratio and LLN criteria for airflow limitation were at signifi-
Significantly increased risk for 7 of the outcomes studied, with particularly strong associations seen for wheeze (OR = 3.25), chronic bronchitis (OR = 3.14), and chronic phlegm (OR = 3.04). Additionally, these patients meeting both criteria also had elevated risk when compared with peers meeting the fixed ratio criterion alone (Table 3).

Modifying Factors and Sensitivity Analysis
Analyses did not reveal any significant interaction between the spirometric criteria for airflow limitation and potential modifying factors such as sex, age, and smoking status. Furthermore, excluding patients with cardiovascular disease did not affect any of the observed associations.

Table 4 shows the impact of the severity of airflow on the associations with patient-reported outcomes in 6 groups of patients stratified by the FEV1/FVC criteria—fixed ratio or LLN—and further by FEV1 status (normal vs low). The results indicated that patients meeting either

### Table 2. Associations Between Airflow Limitation According to Various Criteria and Outcomes

| Outcome               | No Airflow Limitationa (n = 4,038) | Airflow Limitation FR+/LLN– (n = 297) | FR+/LLN+ (n = 532) |
|-----------------------|------------------------------------|--------------------------------------|---------------------|
| Chronic cough         | 1.00                               | 1.40 (0.99-1.98)                     | 2.54 (2.03-3.18)    |
| Chronic phlegm        | 1.00                               | 1.43 (0.97-2.10)                     | 3.04 (2.39-3.87)    |
| Chronic bronchitis    | 1.00                               | 1.59 (0.93-2.72)                     | 3.14 (2.25-4.37)    |
| Wheeze                | 1.00                               | 1.54 (1.15-2.06)                     | 3.25 (2.65-3.97)    |
| MRC dyspnea scaleb    | 1.00                               | 1.14 (0.86-1.52)                     | 2.33 (1.92-2.82)    |
| SF-12 Physical component scalec | 1.00 | –0.78 (0.17)                     | –3.31 (<.01)         |
| SF-12 Mental component scalec | 1.00 | 0.47 (.40)                     | –0.30 (.49)         |
| Exacerbation          | 1.00                               | 1.33 (0.98-1.81)                     | 1.90 (1.54-2.34)    |
| Cardiovascular disease| 1.00                               | 1.52 (1.14-2.04)                     | 1.21 (0.93-1.56)    |

FR = fixed ratio; LLN = lower limit of normal; MRC = Medical Research Council; SF-12 = Short Form 12-item health survey.

Notes: Multiple logistic regression analysis, except as otherwise noted. All models adjusted for age-group (<60 years), sex, and ever smoking. Data are presented as odds ratios (95% CIs) or parameter estimates (P values) from regression analysis. Number of FR–/LLN+ patients was too small for inclusion.

a Reference group (FR–/LLN–).

b Ordinal logistic regression analysis.

c Multiple linear regression analysis.
FEV₁/FVC criterion had higher risks of some clinical outcomes, but the addition of a low FEV₁ to either or both criteria greatly strengthened the associations; patients having such airflow limitation had 2 to 5 times higher odds of most adverse outcomes relative to counterparts having no airflow limitation. Notably, only individuals satisfying either the fixed ratio or LLN criterion (or both) who also had a low FEV₁, indicating moderate to severe airflow limitation, had significantly elevated odds of cardiovascular disease (ORs = 1.51-1.56).

**DISCUSSION**

**Key Findings**

In this study, we found that airflow limitation defined solely by either of the basic criteria for FEV₁/FVC, namely, the fixed ratio or the LLN, was weakly and variably associated with patient-reported poor outcomes such as symptoms, disability, impaired health status, and exacerbations, with stronger associations seen for those meeting the latter criterion. Patients meeting both of these criteria had more consistent and greater increases in risk. But patients meeting either criterion and in addition having a low FEV₁ were the most likely to experience poor outcomes. Cardi...
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using unqualified LLN, these associations were somewhat weaker.20

Our results differ from those of previous studies in several aspects. First, the results indicated that overdiagnosis could be a problem when using a single criterion, either fixed ratio or LLN, as patients with overdiagnosis, having a normal FEV1 (one of at least 80% of predicted), appear to experience few patient-reported outcomes; that is, they do not appear to have clinically relevant disease. This lack of clinical relevance may be related to the fact that COPD found in the population may be milder than that reported in patient cohorts. The diagnosis of COPD in patients with mild disease has been debated before.14,24,25 Second, we found that the associations were modified by the level of lung function. Excluding patients with mild airflow limitation as evidenced by a normal FEV1, the use of either fixed ratio or LLN showed clear and firm associations with symptoms and exacerbations and worsening health status and disability. Third, the significant association between cardiovascular disease and airflow limitation determined by an unqualified fixed ratio criterion may suggest a misdiagnosis of COPD in these patients. Heart failure could potentially mimic airflow obstruction in such patients and raises the question as to whether clinicians should suspect undiagnosed cardiovascular disease in those patients with no or mild airflow limitation (FEV1 ≥80%), especially in the elderly, as determined by fixed ratio only.

Additionally, falsely applying the COPD label to patients with dyspnea who do not have undiagnosed evidence of airflow obstruction can lead to unnecessary and inappropriate treatments. It is conceivable that a high mortality for Group B in the new GOLD classification reflected the circumstance wherein patients had heart disease but were receiving care only for COPD.26 Finally, our results from this study support the use of either fixed ratio or LLN, further qualified by a low FEV1, in the diagnostic confirmation of COPD.

Strengths and Limitations

Although the relationship between diagnostic criteria for COPD and patient-reported outcomes has been previously reported,20 we believe that this is the first study that also includes the evaluation of health status as measured by the SF-12 and examines potential factors that could modify the associations with outcomes. In particular, we systematically assessed the effect of airflow limitation. Although GOLD stage 2 or higher classification has been previously compared with fixed ratio and LLN criteria, our study is the only one to use postbronchodilator spirometry data.27,28 Another strength lies in the derivation of data from the general population and not from a convenience sample of patients as in other published studies. The data come from a large multicenter study that used strict protocols and central data management to ensure that similar measurements across study centers.

There are also several limitations to this study. First, the questionnaire responses in this large epidemiologic study were not clinically confirmed. Second, as the analyzed data were cross-sectional, the diagnostic criteria could not predict outcomes. Last, the subgroup of patients with airflow limitation determined by LLN only was too small for analysis.

Future Directions

Underdiagnosis and overdiagnosis remain challenges to the adequate management of COPD and to the optimal use of health care resources. Given recommendations that diagnosis of COPD be based on the triple criteria of presence of risk factors, symptoms, and spirometric evidence of airflow limitation (a reduced FEV1/FVC) and that the main rationale of pharmacologic treatment of COPD is the reducing symptoms, it could be argued that overdiagnosis rather than underdiagnosis is a more pressing issue in clinical practice. The results of this large cross-sectional study have suggested that a clinically relevant diagnosis of COPD is best based on the use of either cutoff criterion for a low FEV1/FVC coupled with a low FEV1, as percentage of predicted. This impression awaits definitive clarification from longitudinal studies such as the follow-up phase of the ongoing CanCOLD study, in which clinical outcomes in patients having COPD diagnosed using different criteria can be further evaluated.

Conclusions

There is persistent controversy regarding the most appropriate cutoff values for FEV1/FVC in the diagnosis of chronic airflow limitation in COPD. The results from this population-based Canadian study on clinically relevant patient-reported outcomes showed that the use of a single criterion alone—FEV1/FVC either less than 0.7 or less than the LLN—was inadequate and may misdiagnose patients with COPD (in particular those with cardiovascular symptoms), putting them at risk for inappropriate or unnecessary treatments. Our results indicated that a low FEV1/FVC ratio by either the fixed ratio or LLN criterion coupled with a low FEV1 (<80% of predicted) is the most clinically relevant diagnostic criterion for COPD. Future guidelines may reconsider amending the current diagnostic spirometric cutoff to include this additional specification.

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