

Diagnostic accuracy of FEV₁/forced vital capacity ratio z scores in asthmatic patients

Allison Lambert, MD, MHS,^a M. Bradley Drummond, MD, MHS,^a Christine Wei, MS,^a Charles Irvin, PhD,^b

David Kaminsky, MD,^b Meredith McCormack, MD, MHS,^a and Robert Wise, MD^a *Baltimore, Md, and Burlington, Vt*

Background: The FEV₁/forced vital capacity (FVC) ratio is used as a criterion for airflow obstruction; however, the test characteristics of spirometry in the diagnosis of asthma are not well established. The accuracy of a test depends on the pretest probability of disease.

Objective: We wanted to estimate the FEV₁/FVC ratio z score threshold with optimal accuracy for the diagnosis of asthma for different pretest probabilities.

Methods: Asthmatic patients enrolled in 4 trials from the Asthma Clinical Research Centers were included in this analysis. Measured and predicted FEV₁/FVC ratios were obtained, with calculation of z scores for each participant. Across a range of asthma prevalences and z score thresholds, the overall diagnostic accuracy was calculated.

Results: One thousand six hundred eight participants were included (mean age, 39 years; 71% female; 61% white). The mean FEV₁ percent predicted value was 83% (SD, 15%). In a symptomatic population with 50% pretest probability of asthma, optimal accuracy (68%) is achieved with a z score threshold of -1.0 (16th percentile), corresponding to a 6 percentage point reduction from the predicted ratio. However, in a screening population with a 5% pretest probability of asthma, the optimum z score is -2.0 (second percentile), corresponding to a 12 percentage point reduction from the predicted ratio. These findings were not altered by markers of disease control.

Conclusion: Reduction of the FEV₁/FVC ratio can support the diagnosis of asthma; however, the ratio is neither sensitive nor

specific enough for diagnostic accuracy. When interpreting spirometric results, consideration of the pretest probability is an important consideration in the diagnosis of asthma based on airflow limitation. (*J Allergy Clin Immunol* 2015;■■■■:■■■-■■■.)

Key words: Asthma, spirometry, accuracy, z score, airflow obstruction

Asthma is a clinical diagnosis defined by episodic symptoms and environmental triggers. Spirometry is often used to support the diagnosis and to classify the severity of asthma. A diagnosis of airflow obstruction supports a diagnosis of asthma; however, the test characteristics of spirometry in the diagnosis of asthma have not been well defined. Interpretation of spirometric results in asthmatic adults depends on the composition of the reference population, as well as the population being tested.¹ Specifically, according to the Bayes theorem, the diagnostic accuracy of a test depends on the pretest probability or the prevalence of disease in the population being studied.^{2,3} Accordingly, we wanted to understand whether diagnostic criteria for airflow obstruction are helpful in the diagnosis and classification of asthma.

The National Asthma Education and Prevention Program asthma guidelines define asthma as a chronic airway disorder characterized by “variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation.”⁴ The FEV₁/forced vital capacity (FVC) ratio is included as part of the definition of asthma severity, with a ratio more than 5% less than the predicted value as one criterion. However, the rationale for this is not completely elucidated, and the definition of airflow obstruction is controversial. The 1984 Inter-mountain Thoracic Society recommended defining airflow obstruction severity based on FEV₁/FVC ratio strata.⁵ The American Thoracic Society and European Respiratory Society use a lower limit of normal definition to identify airflow obstruction, thereby characterizing disease as an FEV₁/FVC ratio the fifth percentile of a healthy population sample.⁶ The Global Initiative for Asthma defines asthma by combining variable respiratory symptoms with variable expiratory airflow limitation expressed as an FEV₁/FVC ratio of less than 75% to 80%.⁷ Although this might be useful for population screening, it does not take into account the fact that spirometric screening is often performed in a patient population presenting with respiratory symptoms.

The objective of this study was to ascertain the most accurate criterion for the diagnosis of airflow obstruction when there was doubt and the pretest probability was greater than 5% or the prevalence of asthma was greater than that in the general population. We hypothesized that the accuracy of FEV₁/FVC ratio thresholds to diagnose asthma will vary depending on the pretest probability of disease. To accomplish this, we reviewed data from a population with a confirmed physician’s diagnosis

From ^athe Department of Medicine, Division of Pulmonary and Critical Care, Johns Hopkins University, Baltimore, and ^bthe Department of Medicine, Division of Pulmonary and Critical Care, University of Vermont, Burlington.

The Asthma Clinical Research Network is supported by National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) grants 5U10HL051845, 5U10HL051831, 5U10HL051834, 5U10HL051843, 5U10HL056443, 5U10HL051810, and 5U10HL051823.

Disclosure of potential conflict of interest: A. Lambert has been supported by a National Institutes of Health (NIH) training grant (T32 HL007534 32) and has received consultancy fees from GLG Council. C. Irvin is a member of several external advisory committees for NIH grants around the country and has received royalties from UpToDate. M. McCormack has received research support from the NIH/National Institute of Environmental Health Sciences (R21ES 024021 and P50 ES015903) and has received royalties from UpToDate. R. Wise has received consultancy fees from GlaxoSmithKline, Boehringer Ingelheim, Novartis, Astra Zeneca, Teva, Mylan, Spiration, Genentech, Janssen, Bristol Myers Squibb, Pulmonx, Medimmune, Merck, Forest Labs, and Sunovion and has received research support from Pearl Therapeutics, Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Sunovion, and Forest. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 30, 2014; revised February 17, 2015; accepted for publication February 19, 2015.

Corresponding author: Allison Lambert, MD, MHS, 1830 East Monument St, 5th Floor, Baltimore, MD 21205. E-mail: alamber5@jhmi.edu.

0091-6749/\$36.00

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2015.02.027>

Abbreviations used

ALA-ACRC: American Lung Association–Asthma Clinical Research Center
 FVC: Forced vital capacity
 IQR: Interquartile range
 LODO: Effectiveness of Low Dose Theophylline as Add-on Therapy in Treatment of Asthma
 NHANES: National Health and Nutrition Examination Survey

of asthma with varying disease control from the American Lung Association–Asthma Clinical Research Center (ALA-ACRC) and evaluated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the diagnosis of airflow limitation.

METHODS**Study population**

The ALA-ACRC is a network of 20 clinical centers focused on collaborative research aimed at improving asthma care across diverse populations. To characterize the spirometric findings of a well-defined cohort of asthmatic adults, we included enrollment demographic and spirometric data from 4 published ALA-ACRC trials.^{8–11} These trials examined both participants with well-controlled disease (the Leukotriene or Corticosteroid or Corticosteroid-Salmeterol trial⁸) and those with poorly controlled disease (the Effectiveness of Low Dose Theophylline as Add-on Therapy in Treatment of Asthma trial,⁹ Study of Acid Reflux and Asthma,¹⁰ and Trial of Asthma Patient Education¹¹). All patients had a physician's diagnosis of asthma and were prescribed appropriate medications. Full methodologic details of these trials are published elsewhere.^{8–11}

Measurements

Demographic and clinical data were collected from baseline evaluations of participants at the time of enrollment in each study. The Asthma Control Questionnaire (score range, 0–6, with lower scores indicating better controlled asthma)¹² and the Asthma Symptom Utility Index (score range, 0–1, with lower scores indicating more symptomatic asthma)¹³ were used to assess disease control. Spirometric measurements were assessed before any study intervention. Participants enrolled in more than 1 trial contributed data from their most recent trial enrollment.

Defining FEV₁/FVC ratio thresholds

A *z* score is the difference between a measured value and the predicted value normalized to the SD of the predicted population. We calculated FEV₁/FVC ratio *z* score thresholds, which were defined as the difference between measured and predicted FEV₁/FVC ratios divided by the SD of the referent population, using the National Health and Nutrition Examination Survey (NHANES) reference formulae.¹⁴ A *z* score is the number of SDs less than the population mean at which a given individual value falls. The associated reduction in FEV₁/FVC ratios from predicted values for select *z* scores by race and sex are shown in Table E1 in this article's Online Repository at www.jacionline.org. For example, a *z* score of −1.0 (16th percentile) represents a measured FEV₁/FVC ratio 1 SD less than the mean of the predicted ratio and corresponds to about 6 percentage points less than the predicted value. The diagnostic accuracy of FEV₁/FVC ratio *z* score thresholds ranging from −0.5 to −4.5 was calculated.

Statistical analyses

Descriptive data are presented as frequencies, means (SDs) for normally distributed data, and medians (interquartile ranges [IQRs]) for nonnormally

distributed data. The outcome of interest for this analysis was accuracy, which was defined as the sum of true-positive and true-negative test results divided by the total number of persons tested. We constructed an analytic population consisting of disease-free subjects from the NHANES population from whom predicted values were derived and diseased subjects from our observed asthmatic population. We created contingency tables for different prevalences in the population and calculated sensitivity and specificity. We iterated this process across different pretest probabilities (prevalence of disease). Test characteristics were calculated at varying single-tailed FEV₁/FVC ratio *z* score thresholds. Analyses were conducted with Stata software, version 12 (StataCorp, College Station, Tex).

RESULTS**Participants' characteristics**

A total of 1608 participants were included from the 4 trials, of whom 287 (18%) were from the Leukotriene or Corticosteroid or Corticosteroid-Salmeterol trial, 410 (25%) from the Effectiveness of Low Dose Theophylline as Add-on Therapy in Treatment of Asthma trial, 398 (25%) from the Study of Acid Reflux and Asthma, and 513 (32%) from the Trial of Asthma Patient Education (see Table I). The mean age was 40 years (SD, 14 years); 71% were female, and 61% were white. The median Asthma Control Questionnaire score was 1.71 (IQR, 1.00–2.29), and the median Asthma Symptom Utility Index score was 0.80 (IQR, 0.67–0.88). At enrollment, the mean FEV₁ was 83.0% (SD, 15%) of predicted value, and the mean FEV₁/FVC ratio was 0.74 (SD, 0.09). Further characterization of the participants by trial enrollment is included in Table E2 in this article's Online Repository at www.jacionline.org.

Low versus high pretest probability of disease

Because the diagnostic accuracy of a test varies based on the pretest probability of disease, we calculated the test characteristics of different FEV₁/FVC ratio *z* score thresholds at a variety of pretest probabilities. The test characteristics from a broad range of pretest probabilities are reported in Table E3 in this article's Online Repository at www.jacionline.org. Accuracy plateaus as the FEV₁/FVC ratio *z* score threshold decreases for a given pretest probability. To graphically illustrate this plateauing association, we plotted accuracy by FEV₁/FVC ratio *z* score threshold for 3 selected pretest probabilities (5%, 25%, and 50%) in Fig 1. Test characteristics for pretest probabilities of 5% and 50% are presented in Table II because these represent the 2 common and clinically relevant scenarios of using spirometry as a screening test at the population level and of using spirometry as a diagnostic test within a symptomatic subject, respectively. Table II shows that when the pretest probability is 5%, diagnostic accuracy plateaus at an FEV₁/FVC ratio *z* score threshold of −3.0, whereas when the pretest probability is 50%, diagnostic accuracy is optimized at an FEV₁/FVC ratio *z* score threshold of −1.0.

Combining the graphic and tabular data, we defined our recommended FEV₁/FVC ratio *z* score threshold for a given pretest probability as the threshold beyond which only minimal gains in diagnostic accuracy were achieved (Table III). For example, when the pretest probability of asthma is low (5%), as would be the case when conducting spirometry in a general population screening setting, our recommended FEV₁/FVC ratio *z* score threshold was −2.0, which corresponds to a measured FEV₁/FVC ratio 12 percentage points less than the FEV₁/FVC

TABLE I. Clinical and demographic characteristics of asthmatic participants

No. of participants, no. (%)	Total: 1608
LOCCS trial	287 (18)
LODO trial	410 (25)
SARA	398 (25)
TAPE	513 (32)
Age (y), mean (SD)	39.5 (14)
Female sex, no. (%)	1134 (71)
Ethnicity, no. (%)	
Hispanic	134 (8)
Non-Hispanic	1474 (92)
Race, no. (%)	
White	975 (61)
Black	500 (31)
Other	133 (8)
BMI (kg/m ²), median (IQR)	28.7 (24.2-34.6)
Age at asthma diagnosis, median (IQR)	13 (4-30)
Asthma Control Score, median (IQR)	
ACQ-7	1.71 (1.00-2.29)
ASUI	0.80 (0.67-0.88)
FEV ₁ , mean (SD)	
Absolute (L)	2.66 (0.8)
% Predicted	83.0 (15)
FVC, mean (SD)	
Absolute, L	3.60 (1.04)
% Predicted	91.9 (15)
FEV ₁ /FVC, mean (SD)	
Absolute	74 (9)
Predicted	81.9 (4)

ACQ-7, Asthma Control Questionnaire (score range, 0-6); ASUI, Asthma Symptom Utility Index (score range, 0-1); BMI, body mass index; LOCCS, Leukotriene or Corticosteroid-Salmeterol; LODO, Effectiveness of Low Dose Theophylline as Add-on Therapy in Treatment of Asthma; SARA, Study of Acid Reflux and Asthma; TAPE, Trial of Asthma Patient Education.

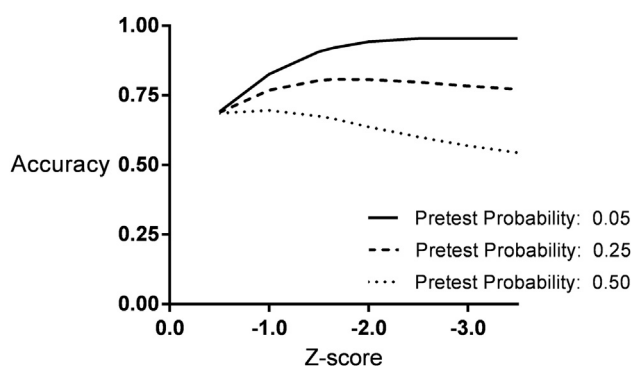


FIG 1. Accuracy by z score FEV₁/FVC ratio threshold for selected pretest probabilities of disease. For a 5% pretest probability of disease (solid line, screening population), optimal accuracy occurs at a z score FEV₁/FVC ratio threshold of -2.0 . For 25% (dashed line) or 50% (dotted line, symptomatic population) pretest probability, the recommended z score FEV₁/FVC ratio thresholds are -1.5 and -1.0 , respectively.

ratio percent predicted value. When the pretest probability of asthma was high (50%), as would be the case in a subject with symptoms, diagnostic accuracy of the FEV₁/FVC ratio was optimized at a z score of -1.0 , which corresponds to a measured FEV₁/FVC ratio 6 percentage points less than the FEV₁/FVC ratio percent predicted value.

TABLE II. Test characteristics at low, intermediate, and high pretest probabilities

Pretest probability	z score	Sensitivity	Specificity	PPV	NPV	Accuracy
0.05	-0.5	0.6803	0.6920	0.1042	0.9763	0.6914
	-1.0	0.5510	0.8410	0.1543	0.9727	0.8265
	-1.5	0.4173	0.9330	0.2469	0.9682	0.9072
	-1.645	0.3825	0.9500	0.2870	0.9669	0.9216
	-2.0	0.2966	0.9770	0.4043	0.9635	0.9430
	-2.5	0.2090	0.9940	0.6470	0.9598	0.9547
	-3.0	0.1399	0.9986	0.8403	0.9566	0.9557
	-3.5	0.0889	0.9998	0.9532	0.9542	0.9542
	-4.0	0.0529	1.0000	0.9893	0.9525	0.9514
	-4.5	0.0286	1.0000	0.9980	0.9514	0.9514
0.25	-0.5	0.6803	0.6920	0.4241	0.8666	0.6891
	-1.0	0.5510	0.8410	0.5360	0.8489	0.7685
	-1.5	0.4173	0.9330	0.6749	0.8277	0.8041
	-1.645	0.3825	0.9500	0.7183	0.8219	0.8081
	-2.0	0.2966	0.9770	0.8113	0.8065	0.8069
	-2.5	0.2090	0.9940	0.9207	0.7903	0.7977
	-3.0	0.1399	0.9986	0.9709	0.7769	0.7839
	-3.5	0.0889	0.9998	0.9923	0.7670	0.7721
	-4.0	0.0529	1.0000	0.9983	0.7600	0.7632
	-4.5	0.0286	1.0000	0.9997	0.7554	0.7571
0.50	-0.5	0.6803	0.6920	0.6884	0.6840	0.6862
	-1.0	0.5510	0.8410	0.7761	0.6519	0.6960
	-1.5	0.4173	0.9330	0.8617	0.6156	0.6751
	-1.645	0.3825	0.9500	0.8844	0.6060	0.6662
	-2.0	0.2966	0.9770	0.9280	0.5814	0.6368
	-2.5	0.2090	0.9940	0.9721	0.5568	0.6015
	-3.0	0.1399	0.9986	0.9901	0.5373	0.5693
	-3.5	0.0889	0.9998	0.9974	0.5232	0.5444
	-4.0	0.0529	1.0000	0.9994	0.5136	0.5264
	-4.5	0.0286	1.0000	0.9999	0.5073	0.5143

Values are presented as proportions. A z score of -1.645 represents the American Thoracic Society/European Respiratory Society recommendation of the lower limit of normal. Boldface values represent recommended FEV₁/FVC ratio z score thresholds. NPV, Negative predictive value (represents the proportion of negative test results that are true-negative results); PPV, positive predictive value (represents the proportion of positive test results that are true-positive results).

TABLE III. Recommended z score thresholds

Pretest probability	Recommended z score threshold*	Percentage points less than predicted FEV ₁ /FVC ratio†
5	-2.0	12
25	-1.5	9
50	-1.0	6

*Based on our assessment of data from Table E1.

†Based on Hankinson et al.¹⁴

Well-controlled versus poorly controlled asthma

We next examined the diagnostic accuracy of a range of FEV₁/FVC ratio z score thresholds at different pretest probabilities among participants with symptomatic poorly controlled asthma (defined by an ACQ score >1.5) and asymptomatic well-controlled asthma (defined by an ACQ score <0.75), as shown in Table IV.¹² We observed findings similar to our analysis with the entire cohort. When the pretest probability was low (5%), diagnostic accuracy plateaued at an FEV₁/FVC ratio z score threshold of -2.0 in both the participants with poorly controlled asthma and those with well-controlled asthma which corresponds

TABLE IV. Test characteristics by degree of asthma control

Pretest probability	z score	Symptomatic poorly controlled asthma (n = 914)*					Asymptomatic well-controlled asthma (n = 253)†				
		Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
0.05	−0.5	0.6915	0.6920	0.1057	0.9771	0.6920	0.6087	0.6920	0.0942	0.9711	0.6878
	−1.0	0.5788	0.8410	0.1608	0.9743	0.8279	0.4625	0.8410	0.1328	0.9675	0.8221
	−1.5	0.4737	0.9330	0.2712	0.9712	0.9100	0.3320	0.9330	0.2069	0.9637	0.9030
	−1.645	0.4398	0.9500	0.3165	0.9699	0.9245	0.2846	0.9500	0.2305	0.9619	0.9167
	−2.0	0.3556	0.9770	0.4486	0.9664	0.9459	0.1897	0.9770	0.3027	0.9582	0.9376
	−2.5	0.2626	0.9940	0.6973	0.9624	0.9574	0.0830	0.9940	0.4213	0.9537	0.9485
	−3.0	0.1816	0.9986	0.8723	0.9587	0.9578	0.0395	0.9986	0.5977	0.9518	0.9506
	−3.5	0.1171	0.9998	0.9640	0.9556	0.9556	0.0198	0.9998	0.8189	0.9509	0.9508
	−4.0	0.0711	1.0000	0.9920	0.9534	0.9535	0.0119	1.0000	0.9541	0.9506	0.9506
	−4.5	0.0383	1.0000	0.9985	0.9518	0.9519	0.0119	1.0000	0.9952	0.9506	0.9506
0.50	−0.5	0.6915	0.6920	0.6918	0.6916	0.6917	0.6087	0.6920	0.6640	0.6388	0.6503
	−1.0	0.5788	0.8410	0.7845	0.6663	0.7099	0.4625	0.8410	0.7441	0.6101	0.6517
	−1.5	0.4737	0.9330	0.8761	0.6394	0.7034	0.3320	0.9330	0.8321	0.5828	0.6325
	−1.645	0.4398	0.9500	0.8979	0.6291	0.6949	0.2846	0.9500	0.8506	0.5704	0.6173
	−2.0	0.3556	0.9770	0.9392	0.6026	0.6663	0.1897	0.9770	0.8919	0.5466	0.5834
	−2.5	0.2626	0.9940	0.9777	0.5741	0.6283	0.0830	0.9940	0.9326	0.5201	0.5385
	−3.0	0.1816	0.9986	0.9924	0.5496	0.5901	0.0395	0.9986	0.9658	0.5097	0.5191
	−3.5	0.1171	0.9998	0.9980	0.5310	0.5584	0.0198	0.9998	0.9885	0.5049	0.5098
	−4.0	0.0711	1.0000	0.9996	0.5184	0.5355	0.0119	1.0000	0.9975	0.5030	0.5059
	−4.5	0.0383	1.0000	0.9999	0.5098	0.5191	0.0119	1.0000	0.9997	0.5030	0.5059

Values are presented as proportions. A z score of −1.645 represents the American Thoracic Society/European Respiratory Society recommendation of the lower limit of normal.

Boldface values represent recommended FEV₁/FVC ratio z score thresholds.

ACQ, Asthma Control Questionnaire; NPV, negative predictive value; PPV, positive predictive value.

*As defined by an ACQ score of greater than 1.5.

†As defined by an ACQ score of less than 0.75.

to a measured FEV₁/FVC ratio 12 percentage points less than the FEV₁/FVC ratio percent predicted value.

When the pretest probability was high (50%), diagnostic accuracy was optimized at an FEV₁/FVC ratio z score threshold of −1.0 in both the participants with symptomatic poorly controlled asthma and those with asymptomatic well-controlled asthma. An FEV₁/FVC ratio z score threshold of −1.0 corresponds to a measured FEV₁/FVC ratio 6 percentage points less than the FEV₁/FVC ratio percent predicted value.

DISCUSSION

Given the dependence of diagnostic accuracy on the pretest probability of disease, we conducted this retrospective analysis of 1608 asthmatic participants from 4 ALA-ACRC trials using a spectrum of asthma pretest probabilities to identify the FEV₁/FVC ratio thresholds offering the greatest accuracy of airflow obstruction diagnosis. In a symptomatic subject with a high pretest probability of disease (50%), a 6 percentage point reduction in the FEV₁/FVC ratio from the predicted ratio yields the best accuracy for diagnosing asthma. In contrast, when screening at the population level represented by a low pretest probability of disease (5%), a 12 percentage point reduction in the FEV₁/FVC ratio would afford the highest accuracy.

The role of pretest probability of disease in the interpretation of pulmonary function test results is underappreciated. The effect of pretest probability has been demonstrated through the comparison of the diagnostic accuracy of cytologic interpretation of bronchial brush specimens by pathologists either with (84%) or without (76%) clinical history information.¹⁵ In a study of the influence of clinical history on the radiologist's reading of mammograms, "alerting history" did not alter the overall diagnostic accuracy of the test but did substantially alter the level

of suspicion of disease, including additional diagnostic and management recommendations, specifically biopsy referral.¹⁶ The classic analysis from the Prospective Investigation of Pulmonary Embolism Diagnosis investigators also incorporated clinical assessment into the interpretation of test results.¹⁷

This study has limitations. Participants enrolled in clinical research trials might not represent the patient presenting for evaluation and undergoing pulmonary function tests for first-time diagnosis of asthma; however, we included participants from a range of studies, enrolling both patients with well-controlled asymptomatic asthma and those with poorly controlled symptomatic asthma. Our cohort did not include participants without asthma, and therefore we were unable to test the accuracy of our recommended FEV₁/FVC ratio thresholds in a population lacking disease; however, the NHANES population was used for construction of the reference population of nonasthmatic subjects, requiring an absence of symptoms, diagnosis of lung disease, and smoking history. Thus this reflects a reasonable group of healthy subjects.

We also recognize that accuracy might not represent the ideal metric when the consequences of false-positive and false-negative results are not equivalent. In other words, when the treatment for the condition has a high cost/benefit ratio, a low false-positive rate is critical.

Although this analysis is largely statistical in nature, we suggest that it could be used in the clinical judgment about whether asthma is present. Specifically, we advise that our findings could be applied to clinical practice in the following ways. When the pretest probability of asthma is low in the clinical setting, as is the case when screening at the population level, using a more specific threshold (eg, a z score of −2.0 or 12 percentage points less than the predicted value) is a more appropriate criterion for airflow limitation. When the pretest

probability of asthma is high in the clinical setting, as is the case when evaluating a symptomatic patient, using a more sensitive z score threshold (eg, a z score of -1.0 or 6 percentage points less than the predicted value) is more appropriate for airflow limitation.

In conclusion, we observed that the most accurate FEV₁/FVC ratio threshold to diagnose asthma varied substantially for differing pretest probabilities. Therefore when interpreting spirometric results, consideration of the pretest probability is critical for the diagnosis of asthma based on airflow limitation.

We thank the ALA-ACRC staff and participants.

Clinical implications: Accuracy depends on pretest probability. When pretest probability is low, a more specific FEV₁/FVC ratio threshold is optimal; when pretest probability is high, a more sensitive FEV₁/FVC ratio threshold should be used.

REFERENCES

- Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. *Chest* 2002;121:1051-7.
- Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ* 2004;329:168-9.
- Hall GH. The clinical application of Bayes' theorem. *Lancet* 1967;2:555-7.
- National Heart, Lung, and Blood Institute. Expert panel report 3 (EPR3): guidelines for the diagnosis and management of asthma, August 2007. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed April 18, 2014.
- Morris AH, Kanner R, Crapo R, Gardner RM. Clinical pulmonary function testing: a manual of uniform laboratory procedures. Salt Lake City (UT): Intermountain Thoracic Society; 1984.
- Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-68.
- Global Initiative for Asthma (GINA). From the global strategy for asthma management and prevention, 2014. Available at: <http://www.ginasthma.org/>. Accessed March 21, 2013.
- American Lung Association Asthma Clinical Research Center, Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007;356:2027-39.
- American Lung Association Asthma Clinical Research Center. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med* 2007;175:235-42.
- American Lung Association Asthma Clinical Research Center, Mastronarde JG, Anthonisen NR, Castro M, Holbrook JT, Leone FT, Teague WG, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med* 2009;360:1487-99.
- Wise RA, Bartlett SJ, Brown ED, Castro M, Cohen R, Holbrook JT, et al. Randomized trial of the effect of drug presentation on asthma outcomes: the American Lung Association Asthma Clinical Research Centers. *J Allergy Clin Immunol* 2009;124:436-44, e1-8.
- Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJ, Pedersen SE. The correlation between asthma control and health status: the GOAL study. *Eur Respir J* 2007;29:56-62.
- Bime C, Wei CY, Holbrook JT, Sockrider MM, Revicki DA, Wise RA. Asthma symptom utility index: reliability, validity, responsiveness, and the minimal important difference in adult asthmatic patients. *J Allergy Clin Immunol* 2012;130:1078-84.
- Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
- Raab SS, Oweity T, Hughes JH, Salomao DR, Kelley CM, Flynn CM, et al. Effect of clinical history on diagnostic accuracy in the cytologic interpretation of bronchial brush specimens. *Am J Clin Pathol* 2000;114:78-83.
- Elmore JG, Wells CK, Howard DH, Feinstein AR. The impact of clinical history on mammographic interpretations. *JAMA* 1997;277:49-52.
- PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA* 1990;263:2753-9.

TABLE E1. Reduction in FEV₁/FVC ratios from predicted values for select z scores by race and sex

z score	Percentage point reduction in FEV ₁ /FVC ratios from predicted values			
	Male		Female	
	White	African American	White	African American
−1.0	5.883*	6.333*	5.954*	6.491*
−1.5	8.825	9.500	8.931	9.737
−2.0	11.766	12.666	11.908	12.982

*Values are calculated from Table 6 of Hankinson et al (Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179-87).

TABLE E2. Clinical and demographic characteristics of participants by ALA-ACRC trial (2000-2013)

	LODO trial	LOCCS trial	TAPE	SARA
Years conducted	2002-2003	2003-2005	2003-2005	2004-2007
No. of participants	489	500	601	412
Age (y), mean $\pm$ SD	40 $\pm$ 15	31 $\pm$ 15	38 $\pm$ 14	41 $\pm$ 13
Participants <18 y old (%)	5	20	5	0
Male sex (%)	26	40	28	32
Former smoker (%)	18	15	14	17
Race or ethnic group (%)				
White	61	61	58	51
Black	29	27	32	39
Hispanic	8	8	7	8
Other	2	3	3	2
Weight status (%)				
Underweight (BMI, <18.5 kg/m ²)	1	1	1	2
Normal weight (BMI, 18.5-24.9 kg/m ²)	27	44	34	20
Overweight (BMI, 25-29.9 kg/m ²)	25	26	27	27
Obese (BMI, $\geq$ 30 kg/m ²)	47	29	38	52
Asthma characteristics (%)				
$\geq$ 1 Urgent visit in prior year	47	34	28	57
$\geq$ 1 Use of oral steroids in prior year	44	29	26	48
Treatment history (%)				
Daily ICS	20	18	17	19
Daily ICS/LABA	51	28	39	81
Daily anti-antileukotriene	6	16	1	26
Daily inhaled short-acting β -agonist	58	30	31	41
Asthma scores (mean $\pm$ SD)				
ASUI score*	0.68 $\pm$ 0.15	0.89 $\pm$ 0.10	0.82 $\pm$ 0.15	0.76 $\pm$ 0.17
Asthma control score†	NC	1.69 $\pm$ 0.81	1.77 $\pm$ 0.77	1.82 $\pm$ 0.81
Pulmonary function (mean $\pm$ SD)				
% Predicted pre-BD FEV ₁	79 $\pm$ 17	86 $\pm$ 14	87 $\pm$ 14	77 $\pm$ 15
% Predicted post-BD FEV ₁	85 $\pm$ 16	97 $\pm$ 13	94 $\pm$ 13	84 $\pm$ 15
FEV ₁ BD response	9 $\pm$ 12	3 $\pm$ 1	9 $\pm$ 11	11 $\pm$ 10
% Predicted pre-BD FVC	107 $\pm$ 18	96 $\pm$ 14	95 $\pm$ 14	87 $\pm$ 15
% Predicted post-BD FVC	112 $\pm$ 18	102 $\pm$ 13	98 $\pm$ 8	92 $\pm$ 14
FVC BD response	5 $\pm$ 11	4 $\pm$ 1	4 $\pm$ 8	6 $\pm$ 8

Data shown represent participants from the individual clinical trials listed. The analytic cohort for our analysis excluded children 18 years of age or less.

ASUI, Asthma Symptom Utility Index; BD, Bronchodilator; LOCCS, Leukotriene or Corticosteroid or Corticosteroid-Salmeterol; LODO, Effectiveness of Low Dose Theophylline as Add-on Therapy in Treatment of Asthma; NC, not collected; SARA, Study of Acid Reflux and Asthma; TAPE, Trial of Asthma Patient Education.

*Higher values indicate less severe asthma. The range for the Asthma Symptom Utility Index is 0 to 1.

†Lower values indicate less severe asthma. The range for the asthma control score is 0 to 7.

TABLE E3. Test characteristics at various pretest probabilities

Pretest probability	z score	Sensitivity	Specificity	PPV	NPV	Accuracy
0.05	−0.5	0.6803	0.6920	0.1042	0.9763	0.6914
	−1.0	0.5510	0.8410	0.1543	0.9727	0.8265
	−1.5	0.4173	0.9330	0.2469	0.9682	0.9072
	−1.645	0.3825	0.9500	0.2870	0.9669	0.9216
	−2.0	0.2966	0.9770	0.4043	0.9635	0.9430
	−2.5	0.2090	0.9940	0.6470	0.9598	0.9547
	−3.0	0.1399	0.9986	0.8403	0.9566	0.9557
	−3.5	0.0889	0.9998	0.9532	0.9542	0.9542
	−4.0	0.0529	1.0000	0.9893	0.9525	0.9514
	−4.5	0.0286	1.0000	0.9980	0.9514	0.9514
0.10	−0.5	0.6803	0.6920	0.1971	0.9512	0.6908
	−1.0	0.5510	0.8410	0.2780	0.9440	0.8120
	−1.5	0.4173	0.9330	0.4090	0.9351	0.8814
	−1.645	0.3825	0.9500	0.4594	0.9326	0.8932
	−2.0	0.2966	0.9770	0.5890	0.9259	0.9090
	−2.5	0.2090	0.9940	0.7946	0.9188	0.9155
	−3.0	0.1399	0.9986	0.9174	0.9127	0.9127
	−3.5	0.0889	0.9998	0.9773	0.9081	0.9087
	−4.0	0.0529	1.0000	0.9949	0.9048	0.9053
	−4.5	0.0286	1.0000	0.9991	0.9026	0.9029
0.15	−0.5	0.6803	0.6920	0.2805	0.9246	0.6903
	−1.0	0.5510	0.8410	0.3795	0.9139	0.7975
	−1.5	0.4173	0.9330	0.5236	0.9007	0.8556
	−1.645	0.3825	0.9500	0.5744	0.8971	0.8649
	−2.0	0.2966	0.9770	0.6948	0.8873	0.8749
	−2.5	0.2090	0.9940	0.8601	0.8769	0.8762
	−3.0	0.1399	0.9986	0.9463	0.8681	0.8698
	−3.5	0.0889	0.9998	0.9856	0.8615	0.8631
	−4.0	0.0529	1.0000	0.9968	0.8568	0.8579
	−4.5	0.0286	1.0000	0.9994	0.8537	0.8543
0.25	−0.5	0.6803	0.6920	0.4241	0.8666	0.6891
	−1.0	0.5510	0.8410	0.5360	0.8489	0.7685
	−1.5	0.4173	0.9330	0.6749	0.8277	0.8041
	−1.645	0.3825	0.9500	0.7183	0.8219	0.8081
	−2.0	0.2966	0.9770	0.8113	0.8065	0.8069
	−2.5	0.2090	0.9940	0.9207	0.7903	0.7977
	−3.0	0.1399	0.9986	0.9709	0.7769	0.7839
	−3.5	0.0889	0.9998	0.9923	0.7670	0.7721
	−4.0	0.0529	1.0000	0.9983	0.7600	0.7632
	−4.5	0.0286	1.0000	0.9997	0.7554	0.7571
0.35	−0.5	0.6803	0.6920	0.5433	0.8008	0.6879
	−1.0	0.5510	0.8410	0.6511	0.7767	0.7395
	−1.5	0.4173	0.9330	0.7703	0.7483	0.7525
	−1.645	0.3825	0.9500	0.8046	0.7407	0.7514
	−2.0	0.2966	0.9770	0.8741	0.7206	0.7389
	−2.5	0.2090	0.9940	0.9494	0.7000	0.7192
	−3.0	0.1399	0.9986	0.9818	0.6832	0.6981
	−3.5	0.0889	0.9998	0.9952	0.6708	0.6810
	−4.0	0.0529	1.0000	0.9989	0.6622	0.6685
	−4.5	0.0286	1.0000	0.9998	0.6566	0.6600
0.50	−0.5	0.6803	0.6920	0.6884	0.6840	0.6862
	−1.0	0.5510	0.8410	0.7761	0.6519	0.6960
	−1.5	0.4173	0.9330	0.8617	0.6156	0.6751
	−1.645	0.3825	0.9500	0.8844	0.6060	0.6662
	−2.0	0.2966	0.9770	0.9280	0.5814	0.6368
	−2.5	0.2090	0.9940	0.9721	0.5568	0.6015
	−3.0	0.1399	0.9986	0.9901	0.5373	0.5693
	−3.5	0.0889	0.9998	0.9974	0.5232	0.5444
	−4.0	0.0529	1.0000	0.9994	0.5136	0.5264
	−4.5	0.0286	1.0000	0.9999	0.5073	0.5143

(Continued)

TABLE E3. (Continued)

Pretest probability	z score	Sensitivity	Specificity	PPV	NPV	Accuracy
0.75	−0.5	0.6803	0.6920	0.8689	0.4192	0.6833
	−1.0	0.5510	0.8410	0.9123	0.3844	0.6235
	−1.5	0.4173	0.9330	0.9492	0.3480	0.5462
	−1.645	0.3825	0.9500	0.9582	0.3390	0.5243
	−2.0	0.2966	0.9770	0.9748	0.3165	0.4667
	−2.5	0.2090	0.9940	0.9905	0.2952	0.4052
	−3.0	0.1399	0.9986	0.9967	0.2790	0.3546
	−3.5	0.0889	0.9998	0.9991	0.2678	0.3166
	−4.0	0.0529	1.0000	0.9998	0.2603	0.2896
	−4.5	0.0286	1.0000	1.0000	0.2555	0.2715

Values are presented as proportions. A z score of −1.645 represents the American Thoracic Society/European Respiratory Society recommendation of the lower limit of normal. NPV, Negative predictive value; PPV, positive predictive value.