



Obstructive and restrictive spirometric patterns: fixed cut-offs for FEV₁/FEV₆ and FEV₆

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ABSTRACT: The purpose of this study was to determine fixed cut-off points for forced expiratory volume in one second (FEV₁)/FEV₆ and FEV₆ as an alternative for FEV₁/forced vital capacity (FVC) and FVC in the detection of obstructive and restrictive spirometric patterns, respectively.

For the study, a total of 11,676 spirometric examinations, which took place on Caucasian subjects aged between 20–80 yrs, were analysed. Receiver–operator characteristic curves were used to determine the FEV₁/FEV₆ ratio and FEV₆ value that corresponded to the optimal combination of sensitivity and specificity, compared with the commonly used fixed cut-off term for FEV₁/FVC and FVC.

The data from the current study indicate that FEV₁/FEV₆ <73% and FEV₆ <82% predicted can be used as a valid alternative for the FEV₁/FVC <70% and FVC <80% pred cut-off points for the detection of obstruction and restriction, respectively. The statistical analysis demonstrated very good, overall, agreement between the two categorisation schemes. For the spirometric diagnosis of airway obstruction (prevalence of 45.9%), FEV₁/FEV₆ sensitivity and specificity were 94.4 and 93.3%, respectively; the positive and negative predictive values were 92.2 and 95.2%, respectively. For the spirometric detection of a restrictive pattern (prevalence of 14.9%), FEV₆ sensitivity and specificity were 95.9 and 98.6%, respectively; the positive and negative predictive values were 92.2 and 99.3%, respectively.

This study demonstrates that forced expiratory volume in one second/forced expiratory volume in six seconds <73% and forced expiratory volume in six seconds <82% predicted, can be used as valid alternatives to forced expiratory volume in one second/forced vital capacity <70% and forced vital capacity <80% predicted, as fixed cut-off terms for the detection of an obstructive or restrictive spirometric pattern in adults.

KEYWORDS: Chronic obstructive pulmonary disease, forced expiratory volume in six seconds, pulmonary function testing, spirometry

Spirometry is the most frequently performed pulmonary function test and is an essential tool for the diagnosis and follow-up of respiratory diseases. Handheld office spirometers are now widely available for use in primary care and improvements in spirometry software have resulted in access to improved spirometric tests. Several studies emphasised the importance of spirometry in primary care, as a screening tool for the early detection of chronic obstructive pulmonary disease (COPD) [1–4]. This has resulted in the need for easy-to-perform spirometry tests. Increasing evidence showed that the forced expiratory volume in six seconds (FEV₆) [5], can be used

as a convenient alternative for forced vital capacity (FVC) [6–9]. The use of six seconds expiratory manoeuvres makes office spirometry easier and faster, providing a more explicit end-of-test definition and reduces the risk of syncope [10].

An important issue in spirometry is the definition of abnormality. The American Thoracic Society and the European Respiratory Society (ERS) guidelines recommend the use of reference equations, derived from a representative sample of healthy subjects, to determine lower limits of normal (LLN) [11, 12], taking into account that the spirometric indices are influenced by age, height, sex and ethnicity. It has already been demonstrated that FEV₁/FEV₆ is a valid alternative for FEV₁/FVC

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when using LLN based on the third National Health and Nutrition Examination Survey (NHANES III) reference equations [6, 7, 9]. At present, spirometers, and in particular handheld spirometers, do not always provide reference equation-based LLN. Moreover, reference equations for FEV₆ and FEV₁/FEV₆ are only available for the USA population (NHANES III survey) [13] and only recently for European subjects in the 65–85-yrs category [14]. Adding to the complexity of the problem, reference equations obtained from different studies lead to significant differences in predicted FVC and FEV₁ [15].

Presently, it is common practice to determine airway obstruction by use of a fixed cut-off point, *i.e.* when FEV₁/FVC is <70%, according to the Guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [16]. The aim of this study is to determine an alternative for the fixed cut-off points of FEV₁/FVC <70% and FVC <80% predicted suitable for the use of FEV₁/FEV₆ and FEV₆, respectively.

METHODS

The data of consecutive adult patients, referred to the lung function laboratory of the Academic Hospital of the University of Brussels (AZ-VUB, Brussels, Belgium), between February 1992 and December 2000, were analysed. Spirometry measurements were performed with a mass-flow sensor (SensorMedics model 2200, Viasys Health Care, Yorba Linda, CA, USA), by highly trained and experienced pulmonary function technicians, according to the guidelines of the ERS [12].

For the diagnosis of airway obstruction, FEV₁/FVC <70% was used as a fixed cut-off point, according to the GOLD guidelines [16]. From a receiver–operator characteristic (ROC) curve, the FEV₁/FEV₆ ratio, that corresponded to the optimal combination of sensitivity and specificity (*i.e.* the greatest sum of both), was determined.

A subject was said to have a restrictive spirometric pattern if there was a reduced FVC in the presence of a normal FEV₁/FVC. A fixed cut-off of 80% of the predicted value for FVC was used as the “gold standard”. The FEV₆ value that corresponded to the optimal combination of sensitivity and specificity was determined from a ROC curve.

To calculate sensitivity and specificity for FEV₁/FEV₆ and FEV₆ as a predictor for obstruction or a restrictive spirometric pattern, 2 × 2 tables were used. For both indices the positive predictive value (PPV) and the negative predictive value

(NPV) were also calculated. The PPV represents the proportion of patients with abnormal test results who have the disease and the NPV represents the proportion of patients with normal test results who do not have the disease. Furthermore, in each analysis the discordant cases, *i.e.* false positives and false negatives, were scrutinised.

Finally, agreement between the two categorisation schemes, based either on FVC or on FEV₆, was assessed using kappa statistics: the number of obstructive patients were determined using FEV₁/FVC <70% as a fixed cut-off point. In the nonobstructive patients, a restrictive spirometric pattern was considered if FVC <80% of the predicted value. Similarly, the cut-offs, obtained by a ROC curve for FEV₁/FEV₆ and FEV₆, were used as a fixed cut-off to determine the number of patients with a normal, obstructive or restrictive spirometric pattern. The resulting classifications, based on either FVC- or FEV₆-related indices, were combined in a 3 × 3 table, and a kappa value was calculated. Kappa represents the agreement between the two categorisation schemes in excess of the amount of agreement that would be expected by chance.

RESULTS

The same study population was used as in a previous study, by the current authors [9], comparing FEV₆ and FVC using LLN determined with the NHANES III reference equations [13]. Spirometric data from 11,676 Caucasian subjects were studied, of whom 7,010 (60%) were male and 4,666 (40%) were female. Subject characteristics are shown in table 1. In this table, FEV₁/FVC <70% and FVC <80% pred were used for the diagnosis of obstruction and a restrictive pattern, respectively.

The obstructive group was further classified into subgroups according to the severity of airway obstruction in accordance with the GOLD guidelines [16]: FEV₁/FVC <70%, in combination with FEV₁ ≥80% pred (Stage I), or 50% ≤ FEV₁ <80% pred (Stage II), or 30% ≤ FEV₁ <50% pred (Stage III), or FEV₁ ≤30% pred (Stage IV).

Spirometric diagnosis of obstruction

Considering FEV₁/FVC <70% as being the ‘gold standard’ for obstruction, a ROC curve was used to determine the best corresponding cut-off for FEV₁/FEV₆ (fig. 1). The area under the ROC curve was 98.8% (95% confidence interval (CI): 98.6–98.9%), and the FEV₁/FEV₆ cut-off, corresponding to the greatest sum of sensitivity and specificity, was 73%. When using a FEV₁/FEV₆ cut-off of 76%, sensitivity reached 100%, but specificity dropped to 71.7%. Choosing a fixed cut-off of

TABLE 1 Subject demographics, presence and severity of airway obstruction

	Subjects n	Age yrs	Height cm	Not obstructed [#]		Obstructed [#]			
				Normal	Restricted [†]	Stage I	Stage II	Stage III	Stage IV
Male	7010	60 (20–80)	173 (142–203)	2826 (40.3)	513 (7.3)	895 (12.8)	1676 (23.9)	826 (11.8)	274 (3.9)
Female	4666	56 (20–80)	163 (135–185)	2550 (54.7)	430 (9.2)	393 (8.4)	844 (18.1)	366 (7.8)	83 (1.8)
Total	11676	59 (20–80)	170 (135–203)	5376 (46.0)	943 (8.1)	1288 (11.0)	2520 (21.6)	1192 (10.2)	357 (3.1)

Data presented as median (range) or n (%) unless otherwise stated. [#]: using forced expiratory volume in one second/forced vital capacity (FVC) <70% as a fixed cut-off.

[†]: using FVC <80% predicted as a fixed cut-off.

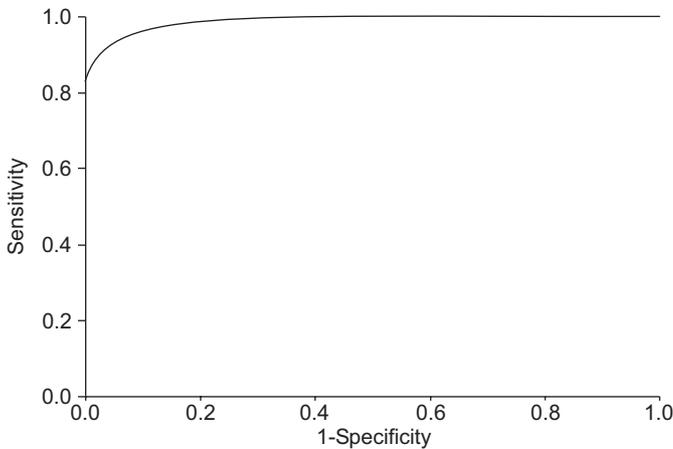


FIGURE 1. Receiver–operator characteristic curve for forced expiratory volume in one second (FEV₁)/FEV₆ using FEV₁/forced vital capacity <70% as a “gold standard” for obstruction.

FEV₁/FEV₆ <70% resulted in a specificity of 100%, with a sensitivity of 84.4%. Table 2 shows the sensitivity and specificity results using FEV₁/FEV₆ <73% as a fixed cut-off. For the total population, FEV₁/FEV₆ sensitivity and specificity were 94.4 and 93.3%, respectively. The PPV and NPV were 92.2 and 95.2%, respectively. The prevalence of obstruction was 45.9%. Similar results were obtained when considering male and female subjects separately (data not shown).

Analysis of the 726 discordant cases (false positives and false negatives combined) showed that 98.8% of the discordant values of FEV₁/FEV₆ are within a ±5% interval of the chosen fixed cut-off of 73%. Only one subject was found to have a FEV₁/FEV₆ which differed by >10% from the cut-off.

In the 426 false positive cases, the mean difference of FEV₁/FVC and FEV₁/FEV₆, with their respective LLN, was 0.9 (SD=1.0) and -2.1% (SD=1.0 %). In the 300 false negative cases the mean difference of FEV₁/FVC and FEV₁/FEV₆ with their respective LLN was -3.6 (SD=2.6) and 1.5% (SD=2.0%).

FEV ₁ /FEV ₆	FEV ₁ /FVC		Totals
	Obstruction [#]	No obstruction [#]	
Obstruction [†]	5057	426	5483
No obstruction [†]	300	5893	6193
Totals	5357	6319	11676

Given as % (95% confidence interval) sensitivity: 94.4 (93.8–95.0); specificity: 93.3 (92.6–93.9); positive predictive value: 92.2 (91.5–92.9); negative predictive value: 95.2 (94.6–95.7); prevalence of obstruction: 45.9%. #: using FEV₁/FVC <70% as a fixed cut-off; †: using FEV₁/FEV₆ <73% as a fixed cut-off.

Spirometric detection of restriction

In all subjects with normal FEV₁/FVC (n=6,319), FVC <80% pred was considered as a ‘gold standard’ for the detection of a restrictive spirometric pattern. A ROC analysis showed that a fixed cut-off of FEV₆ <82% pred resulted in the best combination (*i.e.* greatest sum) of sensitivity and specificity (fig. 2). The area under the ROC curve was 99.5% (95% CI=99.5–99.6%). When using FEV₆ <84% pred, sensitivity reached 100% with a specificity of 95.5%. Choosing FEV₆ <80% resulted in a specificity of 100%, but sensitivity dropped to 88%. Table 3 shows the current findings using FEV₆ <82% pred as a fixed cut-off. For the total population, sensitivity and specificity was 95.9 and 98.6%, respectively. The PPV was 92.2% and the NPV 99.3%. The prevalence of a restrictive pattern was 14.9%. Similar results were obtained for both male and female populations (data not shown).

Analysis of the 116 discordant cases (false positives and false negatives combined) showed that 94.0% of the discordant values of FEV₆ are within a ±5% interval of the chosen fixed cut-off of 82% pred. None of these results differed by >10% with the cut-off (data not shown).

In the 77 false positive cases, the mean difference of FVC and FEV₆, with their respective cut-offs, was 1.1 (SD=1.4) and -2.5% (SD=1.6%). In the 39 false negative cases, the mean difference of FVC and FEV₆ with their respective cut-off was -1.8 (SD=0.8) and 0.5% (SD=0.7%).

Overall agreement using kappa statistics

Overall agreement between the two categorisation schemes was assessed using kappa statistics (table 4). In this study, a kappa value of 0.87 (95% CI=0.86–0.88) was obtained, indicating a very good agreement between FEV₆- and FVC-derived indices.

DISCUSSION

It has already been demonstrated that FEV₆ is a reliable alternative for FVC to identify obstructive and restrictive spirometric patterns, using the NHANES III reference equations to calculate LLN for each spirometric index [7–9]. The

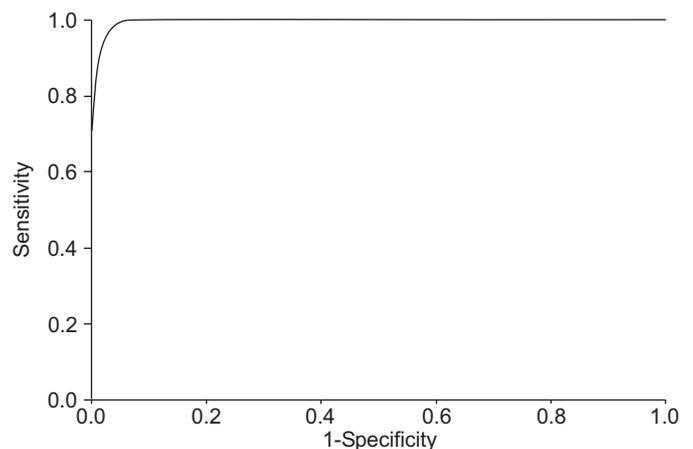


FIGURE 2. Receiver–operator characteristic curve for forced expiratory volume in six seconds using forced vital capacity <80% predicted as a “gold standard” for restriction.

TABLE 3 Comparison of forced expiratory volume in six seconds (FEV₆) with forced vital capacity (FVC) for the diagnosis of a spirometric restrictive pattern: in the nonobstructive group

	FVC		
	Reduced [#]	Normal [#]	Total
FEV ₆ reduced [†]	904	77	981
FEV ₆ normal [†] n	39	5299	5338
Total n	943	5376	6319

Given as % (95% confidence interval) sensitivity: 95.9 (94.4–97.0); specificity: 98.6 (98.2–98.9); positive predictive value: 92.2 (90.3–93.8); negative predictive value: 99.3 (99.0–99.5); prevalence of a restrictive pattern: 14.9%. [#]: using FVC <80% predicted as a fixed cut-off; [†]: using FEV₆ <82% pred as a fixed cut-off.

TABLE 4 Kappa statistics comparing forced expiratory volume in six seconds (FEV₆) and forced vital capacity (FVC) derived indices

	FVC [#]			
	Normal	Obstruction	Restriction	Total
FEV₆[†]				
Normal	4992	226	67	5285
Obstruction	325	5057	101	5483
Restriction	59	74	775	908
Total	5376	5357	943	11676

[#]: using FEV₁/FVC <70% and FVC <80% predicted as fixed cut-offs for an obstructive or restrictive spirometric pattern, respectively; [†]: using FEV₁/FEV₆ <73% and FEV₆ <82% predicted as fixed cut-offs for an obstructive or restrictive spirometric pattern, respectively. Kappa=0.87.

main purpose of the present study was to determine a fixed cut-off for the FEV₁/FEV₆ ratio and for the FEV₆ which are equivalent to the commonly used fixed cut-offs for the FEV₁/FVC ratio and for the FVC.

Indeed, with a kappa value of 0.87, a very good overall performance was obtained for FEV₁/FEV₆ <73% and FEV₆ <82% pred as fixed cut-offs for the detection of obstructive and restrictive spirometric patterns, respectively (table 4). A kappa value of 1 indicates perfect agreement, while a kappa value of 0 indicates that agreement is no better than chance. LANDIS and KOCH [17] have proposed the following as standards for strength of agreement for the kappa coefficient: 0.01–0.20=slight, 0.21–0.40=fair, 0.41–0.60=moderate, 0.61–0.80=substantial and 0.81–1=almost perfect agreement.

Spirometric diagnosis of obstruction

A ROC curve analysis showed that FEV₁/FEV₆ <73% was the cut-off with the best combination of sensitivity and specificity, and performed well as a surrogate for FEV₁/FVC <70% (table 2). In addition, almost all of the discordant cases were close to the cut-off value.

The findings of the present study apply to a population with an overall prevalence of airway obstruction of 45.9%, which corresponds to reported prevalences of COPD of 30–50% in high-risk populations, *i.e.* smokers aged >45 yrs and subjects with respiratory symptoms. This makes FEV₁/FEV₆ suitable for screening purposes in primary care.

It should be emphasised that fixed cut-off values should be used with caution, as spirometric indices are highly influenced by age, height, sex and race. From the NHANES III survey, reference equations have become available to calculate predictive values and LLN for FEV₁, FVC, FEV₆, FEV₁/FVC and FEV₁/FEV₆, with age and height as predictor variables [13]. In the study by HANKINSON *et al.* [13], the analysis was performed separately for each sex and each ethnic group, and the LLN was estimated as predicted minus 1.645 times the standard error of the estimate, which corresponds to the fifth percentile.

While fixed cut-off values are more widely used, in an attempt to simplify the diagnosis, there is potential for misclassification. For example, in elderly subjects, where the age-related decline in FEV₁/FVC and FEV₁/FEV₆ may cause a significant

TABLE 5 Age and sex dependency of the lower limits of normal (LLN)[#] for forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) and FEV₁/FEV₆

Age yrs	Male				Female			
	FEV ₁ /FVC	Δ FEV ₁ /FVC	FEV ₁ /FEV ₆	Δ FEV ₁ /FEV ₆	FEV ₁ /FVC	Δ FEV ₁ /FVC	FEV ₁ /FEV ₆	Δ FEV ₁ /FEV ₆
20	74.3	4.3	75.6	2.6	76.8	6.8	78.2	5.2
30	72.2	2.2	74.2	1.2	74.6	4.6	76.6	3.6
40	70.1	0.1	72.8	-0.2	72.5	2.5	75.1	2.1
50	68.1	-1.9	71.5	-1.5	70.4	0.4	73.5	0.5
60	66.0	-4.0	70.1	-2.9	68.3	-1.7	71.9	-1.1
70	63.9	-6.1	68.7	-4.3	66.1	-3.9	70.4	-2.6
80	61.9	-8.1	67.3	-5.7	64.0	-6.0	68.8	-4.2

Data presented as % predicted. Δ FEV₁/FVC: difference between the LLN and the fixed cut-off FEV₁/FVC <70%; Δ FEV₁/FEV₆: difference between the LLN and the fixed cut-off FEV₁/FEV₆ <73%. [#]: LLN based on the third National Health and Nutrition Examination Survey reference equations for Caucasian subjects [13].

TABLE 6 Age and height dependency of the lower limits of normal (LLN)[#] of forced vital capacity (FVC) and forced expiratory volume in six seconds (FEV₆) in males

Age yrs	Height cm											
	165				175				185			
	FVC LLN	FVC % pred	FEV ₆ LLN	FEV ₆ % pred	FVC LLN	FVC % pred	FEV ₆ LLN	FEV ₆ % pred	FVC LLN	FVC % pred	FEV ₆ LLN	FEV ₆ % pred
20	4.0	83	4.0	84	4.5	83	4.5	84	5.1	83	5.1	84
30	3.9	83	3.8	83	4.4	83	4.3	83	5.0	83	4.9	83
40	3.7	82	3.6	82	4.2	82	4.1	82	4.8	83	4.7	83
50	3.4	81	3.3	81	4.0	81	3.8	81	4.5	82	4.4	82
60	3.1	80	3.0	79	3.7	80	3.5	80	4.2	81	4.0	80
70	2.8	78	2.6	77	3.3	79	3.1	78	3.9	79	3.7	79
80	2.4	75	2.2	74	2.9	77	2.7	75	3.5	78	3.3	77

% pred: percentage of predicted. [#]: LLN based on the third National Health and Nutrition Examination Survey reference equations for Caucasian subjects [13].

TABLE 7 Age and height dependency of the lower limits of normal (LLN)[#] of forced vital capacity (FVC) and forced expiratory volume in six seconds (FEV₆) in females

Age yrs	Height cm											
	155				165				175			
	FVC LLN	FVC % pred	FEV ₆ LLN	FEV ₆ % pred	FVC LLN	FVC % pred	FEV ₆ LLN	FEV ₆ % pred	FVC LLN	FVC % pred	FEV ₆ LLN	FEV ₆ % pred
20	2.8	82	2.8	82	3.2	82	3.2	82	3.6	82	3.6	82
30	2.8	82	2.8	82	3.2	82	3.2	82	3.6	82	3.6	82
40	2.7	81	2.7	81	3.1	81	3.0	81	3.5	81	3.4	81
50	2.6	80	2.5	80	2.9	81	2.9	80	3.4	81	3.3	81
60	2.3	79	2.2	78	2.7	79	2.6	79	3.1	80	3.0	79
70	2.0	76	1.9	75	2.4	77	2.3	77	2.8	78	2.7	77
80	1.6	72	1.5	71	2.0	74	1.9	73	2.4	75	2.3	74

% pred: percentage of predicted. [#]: LLN based on the third National Health and Nutrition Examination Survey reference equations for Caucasian subjects [13].

over-diagnosis of airway obstruction, pointed out by HARDIE *et al.* [18]. This is illustrated here by table 5 where LLN values, derived from the NHANES III reference equations, are depicted for discrete ages between 20–80 yrs. Clearly, fixed cut-offs of FEV₁/FVC <70% and FEV₁/FEV₆ <73% are most suitable for use with middle-aged subjects. Table 5 also shows that cut-offs could be 7% (for FEV₁/FVC) or 5% (for FEV₁/FEV₆) higher in 20-yr-old females and 8% (for FEV₁/FVC) or 6% (for FEV₁/FEV₆) lower in 80-yr-old males. Finally, it must be considered that, regardless of the method used to define abnormality, measured values that lie close to the threshold should be interpreted with caution, due to several sources of variability: 1) diurnal and day-to-day variations of spirometric indices [11]; 2) between-manoeuvre repeatability criteria that allow for a difference up to a maximum of 0.150 L between the two largest values of both FEV₁ and FVC [5]; 3) patients with obstruction having coefficients of variation for FEV₁ and FVC that are approximately twice those of normal subjects [19].

Spirometric detection of restriction

The present study shows that the commonly used cut-off value, FVC <80% predicted, could be replaced by FEV₆ <82% pred, especially for excluding a restrictive ventilatory defect. However, a restrictive abnormality is characterised by a reduced total lung capacity, whereas a reduced FVC in the presence of a normal FEV₁/FVC can only be used to suggest, but not to diagnose, the presence of a restrictive abnormality [11]. A study by SWANNEY *et al.* [8] showed that spirometry-based algorithms could not reliably predict a reduced total lung capacity, but are very useful at excluding a restrictive defect. They also demonstrated that FEV₆ was equivalent to FVC when using LLN calculated with the NHANES III reference equations. In the current study high, negative predictive values were found when comparing FEV₆ and FVC as a predictor of a restrictive pattern (table 3). This makes the use of FEV₆ suitable for the exclusion of restriction.

However, fixed percentages of the predicted value should be used with caution. Tables 6 and 7 show the age and height dependency of the LLN for FVC and FEV₆, using the NHANES III reference equations, for males and females. Using fixed cut-offs had a tendency towards over-diagnosis of a restrictive pattern in elderly people.

CONCLUSION

This study demonstrates that forced expiratory volume in one second/forced expiratory volume in six seconds <73% and forced expiratory volume in six seconds <82% pred can be used as a valid alternative for forced expiratory volume in one second/forced vital capacity <70% and forced vital capacity <80% pred as fixed cut-off points for the detection of an obstructive or restrictive spirometric pattern in adults. The authors emphasise that the fixed cut-off terms should be used with caution, particularly outside the middle-aged population. Ideally, abnormalities in spirometric values should be defined using lower limits of normal, derived from a representative sample of healthy subjects.

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