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Review Article

Revitalizing the Standardization of Criteria for Diagnosing Obstructive Ventilatory Impairment: A Crucial Call to Scholarly Societies (ATS, ERS, GINA, and GOLD) for Action

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Abstract

The diagnosis of obstructive ventilatory impairment (OVI) is currently lacking worldwide consensus. This lack of agreement on the threshold for a significantly low ratio of forced expiratory volume in 1 second to forced vital capacity has led to ongoing debates and misperception among physicians and researchers. This review aims to update the definitions of OVI provided by scholarly societies, including the American Thoracic Society and European Respiratory Society (ATS/ERS), the Global Strategy for Prevention, Diagnosis, and Management of COPD (GOLD), and the Global Initiative for Asthma (GINA). Additionally, the review provides an overview of the rationales behind these definitions and highlights the challenges associated with spirometric indices and threshold selection. The call to action urges scholarly societies to standardize the criteria for diagnosing OVI. Two approaches were used by scholarly societies to define OVI: the physiological approach (ATS/ERS) and the operational approach (GOLD and GINA). Each approach utilizes different criteria and threshold values for diagnosing OVI, creating complexity for clinicians and researchers. The advantages and limitations of the physiological and operational approaches are discussed. The physiological approach offers increased specificity, early detection, and reduced false positives, but challenges in interpretation and limited application should be considered.The operational approach provides simplified diagnosis, aligns with clinical trial evidence, and facilitates screening and case finding. However, it increases the risk of misdiagnosis, it may lead to misclassification and challenges in interpreting results for different age groups, variability with sex and height, and potential misdiagnosis and adverse outcomes. It is recommended that ATS/ERS, GOLD, and GINA work towards proposing a standardized definition for OVI. By doing so, healthcare professionals can ensure consistent and effective diagnosis and management of OVI, ultimately improving patient care and outcomes.

Keywords: *Bronchial Asthma; Bronchial Obstruction; COPD; Diagnostic Criteria; Physiological Approach; Operational Approach; Spirometry*

Abbreviations

ATS: American Thoracic Society; COPD: Chronic Obstructive Pulmonary Disease; ERS: European Respiratory Society; FEV_x: Forced Expiratory Volume in x Second; FVC: Forced Vital Capacity; GINA: Global Initiative for Asthma; GLI: Global Lung Function Initiative; GOLD: Global

Strategy for Prevention, Diagnosis, and Management of COPD; LLN: Lower Limit of Normal; OVI: Obstructive Ventilatory Impairment; SVC: Slow Vital Capacity

Introduction

The global prevalence of chronic obstructive pulmonary disease (COPD) and bronchial asthma is steadily increasing [1,2]. Both of these chronic diseases are characterized by obstructive ventilatory impairment (OVI), which necessitates the use of precise diagnostic methods such as spirometry [1-3]. Conventionally, the diagnosis of OVI is based on an abnormally low ratio between forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) [1-9]. The presence of a significantly low FEV_1/FVC ratio is considered the gold standard for confirming the diagnosis of OVI [1-9]. However, there is currently no worldwide consensus on what constitutes a significantly low FEV_1/FVC ratio [1-9]. As of June 13, 2023, there is a lack of agreement on the threshold that best defines a significantly low ratio, leading to ongoing debates [1-9]. Consequently, the medical community lacks a clear consensus on the definition and criteria for identifying OVI, causing misperception and potential misdiagnosis for physicians and pulmonary researchers [4,10-12].

The aims of this review were to i) Update the definitions of OVI used by various scholarly societies, including the American Thoracic Society and European Respiratory Society (ATS/ERS) [3], the Global Strategy for Prevention, Diagnosis, and Management of COPD (GOLD) [1], and the Global Initiative for Asthma (GINA) [2]; and ii) Provide a brief overview of the rationales behind the different definitions [1-3]. This review serves as a crucial call to scholarly societies such as ATS/ERS, GINA, and GOLD, urging them to take action and revitalize the standardization of criteria for diagnosing OVI.

How scholarly societies define OVI in 2023?

Scholarly societies have established two approaches to define OVI: a physiological approach (ATS/ERS) [3] and an operational approach (GOLD and GINA) [1,2] (Box 1). The ATS/ERS [3] utilizes a physiological approach by defining OVI as a FEV_1/FVC ratio under the 5^{th} percentile [i.e. lower limit of normal (LLN) range or a z-score < -1.645] derived from reference values that consider age and sex [13]. The ATS/ERS [3] suggests adjusting the LLN lower when spirometry is performed in low-risk populations, such as general screening, to reduce the number of false positives. They propose conservative LLNs of 2.5% (z-score <-1.965) or even 1% (z-score < -2.326) [3]. GOLD adopts an operational approach, using a fixed value of 0.70 (post-bronchodilator FEV_1/FVC < 0.70) [1]. However, GOLD provides further guidance for two scenarios related to the initial value of the post-bronchodilator FEV_1/FVC ratio measured on a single spirometric test [1]. First, if the ratio falls between 0.60 and 0.80, OVI should be established by repeat spirometry on a distinct visit to account for biological variation [1]. Second, when the initial ratio is <0.60, it is highly improbable to increase naturally above 0.70, and the diagnosis of OVI (and therefore COPD) is confirmed [1]. GINA follows an operational approach using fixed threshold values of 0.75 to 0.80 in adults and 0.90 in children [2]. GINA recommends comparing the reduced FEV_1 with the LLN and confirming that the FEV_1/FVC ratio is typically > 0.90 in children and > 0.75 - 0.80 in adults [2] based on the multi-ethnic reference values for spirometry established by the Global Lung Function Initiative (GLI) 2012 equations [13]. These three different definitions have created complexity for clinicians and researchers alike.

Rationales behind the retained definitions?

The following three points need to be briefly highlighted: i) Should we use FEV_1/FVC or FEV_1/slow vital capacity (SVC) as the preferred spirometric index for assessing OVI? ii) Are there other alternative spirometric indices that have been proposed to assess OVI? And iii) Which approach (physiological or operational) and which threshold to apply?

FEV_1/FVC or FEV_1/SVC?

Among the discussed three scholarly societies, only ATS/ERS [3] addresses the use of FEV_1/SVC in assessing OVI (Box 1).

Scholarly societies, Year	Approach and definition	Alternative indices

ATS/ERS 2022 [3]	• Physiological approach: z-score FEV_1/FVC:
	  • < -1,645: Individuals with elevated risk
	  • < -1,96 or < -2.326: Screening the general population
		• FEV_1/SVC?
		• FEV_1/FEV_6?
		• FEV_1/FEV_3?
		• FEV_1/FEV_2?
		• FEV3/FV6?
		• FEV3/FVC?
		• Inspiratory capacity
		• Flow-volume loop' slope
		• Flow-volume loop' curvature
		• Raw, sRaw, sGaw: body plethysmography
		• Oscillometry

GOLD 2023 [1]	• Operational approach: Post-BD FEV_1/FVC < 0.70
	• 2 situations related to the initial value of the post-BD FEV_1/FVC ratio:
	  • Between 0.60 and 0.80: OVI should be confirmed by repeat spirometry on a separate occasion
	  • < 0.60: OVI retained
		• Not applied

GINA 2023 [2]	• Operational approach: FEV_1/FVC
	  • < 0.75: Adults
	  • < 0.90: Children
		• Not applied

ATS/ERS: American Thoracic Society and European Respiratory Society; BD: Bronchodilator; FEV_x: Forced Expiratory Volume in x Second; FVC: Forced Vital Capacity; GINA: Global Initiative for Asthma; GOLD: Global Strategy for Prevention, Diagnosis and Management of Chronic Obstructive Pulmonary Disease; Raw: Airway Resistance; sGaw: Specific Airway Conductance; sRaw: Specific Raw; SVC: Slow Vital Capacity.		

Box 1: *Definitions of obstructive ventilatory impairment (OVI) according to some scholarly societies.*

According to ATS/ERS [3], using the largest vital from either SVC or FVC in place of FEV_1/FVC for diagnosing OVI may increase sensitivity but decrease specificity compared to FEV_1/FVC [14]. In healthy individuals, FVC and SVC do not significantly differ [13]. However, if SVC exceeds FVC by more than 100 mL, it suggests airway collapse during forced exhalation [3]. The use of FEV_1/SVC to diagnose OVI introduces uncertainty, particularly in the older population. Therefore, ATS/ERS [3] recommends using FVC for the FEV_1/FVC ratio because i) Both measurements should be obtained from forced expiratory maneuvers using identical equipment, and ii) Accurate norms are available for FEV_1/FVC but not for FEV_1/SVC.

Utility of some alternative spirometric indices assessing OVI

Among the discussed scholarly societies, only ATS/ERS [3] addressed the utility of alternative spirometric indices for assessing OVI (Box 1). First, ATS/ERS [3] suggests that some forced expiratory volume in x seconds, such as FEV_6, FEV_3, or FEV_2, may be used as substitutes for FVC and show accuracy in diagnosing OVI, provided appropriate LLNs for FEV_1/FEV_6, FEV_1/FEV_3, and FEV_1/FEV_2 are used (which is not the case with the GLI equations) [13]. Second, ATS/ERS [3] introduces inspiratory capacity, derived from spirometry, as another measure of OVI. Third, ATS/ERS [3] describes several other indices resulting from examination of the forced expiratory maneuver, including data of the slope or curvature of the flow/volume loop. Fourth, ATS/ERS [3] reports that additional measurements of airway function obtained through body plethysmography (e.g. airway resistance, specific airway resistance, or specific airway conductance) may complement spirometry in assessing OVI, particularly in children and individuals with early signs of lung disease, where spirometry values can appear normal despite confirmed disease. However, as stated by ATS/ERS [3], these measurements are not commonly used for identifying OVI. Finally, in individuals incapable to achieve a maximal forced expiratory maneuver, ATS/ERS [3] suggests that measuring respiratory system resistance using non-invasive oscillometry procedures may be useful.

Which approach and which threshold to apply?

For each approach, its rational, its strong points (advantages) and its limitations (inconvenient) will be discussed below (Box 2). It is important to note that the advantages and limitations provided in box 2 are general observations and may not cover all specific aspects or considerations associated with each approach. The choice between the operational and physiological approaches should be carefully considered, taking into account the specific clinical context and available evidence.

	Physiological approach (ATS/ERS [3])	Operational approach (GOLD [1], GINA, [2])
Rationale	• Compares individual spirometry parameters with reference values	• Uses fixed threshold values for diagnosing OVI
Strong points	• Increased specificity: Considers age-related changes in the FEV_1/FVC ratio, leading to greater specificity in diagnosing OVI • Early detection: Capable of detecting OVI in the early stages, especially in younger adults or children, before the FEV_1/FVC falls below the fixed threshold of 0.70. • Reduced false positives: Leads to fewer false-positive diagnoses in the elderly population, where the FEV_1/FVC naturally decreases due to aging.	• Simplified diagnosis: Easy to remember and apply in clinical practice, providing consistency across different settings. • Clinical trial evidence: Aligns with variables measured in clinical trials, facilitating translation of research findings into practice. • Screening and case finding: Serves the purpose of quick assessment of OVI across different age groups by general practitioners and specialists. • Limited risk of misdiagnosis: Acknowledges that spirometry is only one component of clinical diagnosis, reducing risk of misdiagnosis and over-treatment based solely on spirometry results.

Limitations	• Challenges in interpretation: Literal interpretation of functional impairment may be too simplistic when FEV_1/FVC ratio is close to the LLN • Limitation of application: Lack of spirometric norms for many countries, but the GLI multi-ethnic reference equations have addressed this limitation. • Errors in interpretation: LLN values highly dependent on the choice of reference equations and race/ethnicity	• Age-related variations: May under-diagnose OVI in young adults and over-diagnose it in the elderly, particularly in mild disease. • Variability with sex and height: Fixed cutoffs do not account for observed changes in FEV_1/FVC ratio variability with sex and height, potentially resulting in misinterpretation for women. • Misdiagnosis and adverse outcomes: Potential underdiagnosis and adverse outcomes when individuals classified as having OVI based on physiological approach but not meeting operational approach. • Presence of inexpensive pocket spirometers: The argument that fixed cutoffs are easy to remember is not justified, as even inexpensive pocket spirometers compute predicted FEV_1 and FEV_1/FVC, as well as the LLN. • Conflict with reference data: Thresholds proposed by GINA conflict with statements from the GLI, which discourages the use of fixed thresholds due to age, height, and sex biases. The GINA thresholds also do not consider the biphasic trend of FEV_1/FVC ratio in childhood and adolescence.
ATS/ERS: American Thoracic Society and European Respiratory Society; FEV_1: Forced Expiratory Volume in1 Second; FVC: Forced Vital Capacity; GINA: Global Initiative for Asthma; GOLD: Global Strategy for Prevention, Diagnosis and Management of Chronic Obstructive Pulmonary Disease.		

Box 2: *Rational, strong points and limitations of the physiological and operational approaches adopted to define an obstructive ventilatory impairment (OVI) according to some scholarly societies.*

Physiological approach: ATS/ERS [3]

The physiological approach adopted by ATS/ERS [3] for interpreting spirometry data is based on comparing individual parameters with reference values [15]. In this approach, values below the LLN, defined as the 5^{th} percentile, are qualified abnormally low [3]. This method is appropriate as it focuses on determining whether the calculated FEV_1/FVC ratio is significantly low. This approach has several arguments supporting its use but also has limitations that should be considered.

Advantages of the physiological approach include:

i) **Increased specificity:** By considering age-related variations in the FEV_1/FVC ratio [13], the physiological approach offers greater specificity in diagnosing OVI.

ii) **Early detection:** The approach is capable of detecting OVI in the early stages of the disease, especially in younger adults or children, before the FEV_1/FVC falls below the fixed threshold of 0.70 [6].

iii) **Reduced false positives:** In the elderly population, where the FEV_1/FVC naturally decreases below 0.70 due to aging, the physiological approach leads to fewer false-positive diagnoses [16].

Limitations of the physiological approach include:

i) **Challenges in interpretation:** Challenges arise when the FEV_1/FVC ratio is close to its LLN [15]. In such cases, a literal reading of functional impairment may be too basic, and additional tests, such as bronchodilator testing, should be performed to provide a more comprehensive assessment [15].

ii) **Limitation of application:** The use of the physiological approach may be limited by the absence of spirometric norms for numerous countries [4,17], although the GLI multiethnic reference equations recommended since 2012 have addressed this limitation [13]. The GLI equations, based on data from a large and diverse population, provide more precise definitions of LLN using z-scores and are independent of ethnicity except for South East Asians [13].

iii) **Errors in interpretation:** Since the LLN depends on the reference equation used for the interpretation [18,19], errors in interpretation can occur if inappropriate norms are used [18]. According to GOLD [1], LLN values depend on the norms as well as ethnicity/race, and there is a lack of longitudinal studies certifying the use of the LLN.

In summary, while the physiological approach offers advantages such as specificity, early detection, and reduced false positives, challenges related to interpretation near the LLN and the availability of appropriate reference equations should be considered. The use of the GLI equations has improved the application of the physiological approach in diverse populations [13].

Operational approach: GOLD [1] and GINA [2]

The operational approach, as advocated by GOLD [1] and GINA [2], relies on fixed threshold values for diagnosing OVI. This approach utilizes a similar rationale as the one used for diagnosing other chronic conditions like arterial hypertension or diabetes mellitus, where it is established that using fixed cut-offs is effective [20], so that a fixed cut-off for FEV_1/FVC should also yield reliable results [21]. However, normal blood pressure and glucose levels are tightly regulated within a narrow range by physiological control mechanisms. In contrast, there is no comparable system governing the level of FEV_1/FVC, leading to the acceptance that there is no specific target value for FEV_1/FVC [20].

The GINA proposed thresholds for adults and children have been approximately derived from the curve displaying the mean FEV_1/FVC as a function of age [2]. This operational approach, which is widely used in clinical studies [6], has several advantages but also some limitations that should be considered.

Advantages of the operational approach include:

i) **Simplified diagnosis:** The use of a single number (e.g. 0.70 for GOLD [1], 0.75 and 0.90 for GINA [2]) makes the diagnosis of OVI easy to remember and apply in clinical practice [22]. This simplicity is valued by busy clinicians [22] and allows for consistency across different settings. These qualities lend the 0.70 threshold, for example, to practical use in the recognition of COPD in any state [10].

ii) **Clinical trial evidence:** The operational approach aligns with the variables measured in clinical trials, which form the basis for treatment recommendations [1]. This consistency facilitates the translation of research findings into clinical practice [1]. The usage

of the operational approach is linked with augmented mortality, while the usage of the physiological one is not [23]. In this regard, it has been shown that individuals who were classified as having an OVI using a fixed threshold (i.e. 0.70) but normal using the 5th percentile had a high probability of disease with more respiratory symptoms, a significantly lower diffusion capacity, more exertional dyspnoea and poor exercise tolerance, more emphysema, gas trapping and airway wall thickening on computed tomography than those without OVI [9,24,25]. These results are in favour of the superiority of the operational approach over the physiological approach at least for the COPD diagnosis. Moreover, using the operational approach (e.g. fixed ratio) is not inferior to the physiological approach (e.g. LLN) regarding prognosis [26].

iii) **Screening and case finding:** The operational approach serves the purpose of screening by providing a quick assessment of OVI. It can be used across different age groups by general practitioners and specialists from other disciplines.

iv) **Limited risk of misdiagnosis:** The operational approach acknowledges that spirometry is only one component of the clinical diagnosis of OVI, and additional assessments are necessary to establish a comprehensive evaluation. This reduces the risk of misdiagnosis and over-treatment based solely on spirometry results.

In 2010, a letter was sent to GOLD criticizing the operational approach, and the signatories urged committee members to abandon this approach in favor of the physiological approach [27-31]. Limitations of the operational approach include:

i) **Age-related variations:** The fixed threshold values, such as 0.70 for FEV_1/FVC, may over-diagnose OVI in the elderly, particularly in mild disease, and under-diagnose it in young adults [1]. This leads to potential misclassification and challenges in interpreting results for different age groups including elderly subjects and children [1]. The ATS/ERS [3] strongly discouraged the use of the 0.70 threshold for the FEV_1/FVC ratio, and qualified it as a "rule of thumb". The 0.70 threshold only approximates the LLN in the mid-range of age, where case finding of OVI or screening it is most likely to be performed. The LLN drops under a ratio of 0.70 from 45 years of age [27-31]. By disregarding the fact that the FEV_1/FVC ratio naturally varies with age, even among non-smokers who have remained healthy throughout their lives [32], the prevalence of OVI is underestimated in younger individuals and overestimated in older individuals [4,16,33,34]. The 0.70 cut-offs causes up to 50% over-diagnosis above 45 years of age [27-31], and leaded to systematic misinterpretation of results for children [3]. In other studies, it appaears that the fixed threshold resulted in underdiagnosis of COPD whatever the age was [4].

ii) **Variability with sex and height:** The fixed cutoffs do not account for the observed changes in FEV_1/FVC ratio variability with sex and height [35]. For instance, the use of 0.70 cut-off resulted in consistent misinterpretation of results for women [3].

iii) **Misdiagnosis and adverse outcomes:** Some studies have shown that individuals classified as having OVI based on the physiological approach (i.e. FEV_1/FVC ratio < 5th percentile) but not meeting the operational approach (i.e. FEV_1/FVC ratio > 0.70) exhibit symptoms and markers of disease, suggesting potential underdiagnosis and adverse outcomes. This raises concerns about the superiority of the operational approach over the physiological approach [7,8].

iv) **Presence of inexpensive pocket spirometers:** The justification for using fixed cutoffs of 0.70, 0.75, and 0.90 based on their ease of memorization is unfounded since even affordable pocket spirometers calculate predicted values for FEV_1 and FEV_1/FVC, as well as the LLN [20].

v) **Conflict with reference data:** The thresholds proposed by GINA [2] (Box 1) conflict with statements from the GLI [13], which discourages the use of fixed thresholds due to age, height, and sex biases. The GINA thresholds fail to take into account the biphasic trend observed in the FEV_1/FVC during growth (i.e. childhood and adolescence) [13]. In practice, the 5th percentile for FEV_1/FVC vary with age and is clearly different from the threshold values proposed by GINA [2].

In conclusion, the operational approach has advantages such as simplicity and consistency but is also associated with limitations related to age-related variations, lack of physiological regulation, misdiagnosis, and conflict with reference data.

What should be done in future?

In the future, the following actions are recommended:

i) **Conduct higher-quality prospective studies [3,17,36]:** More research is needed to clearly define what constitutes an OVI, considering the smoking status of individuals [4,10,11]. These studies should aim to establish an unambiguous consensus on OVI diagnosis and compare different approaches in terms of their effectiveness in identifying the disease.

ii) **Comparative analysis of different definitions:** It is important to compare the various diagnostic approaches and definitions in terms of their ability to accurately identify individuals with OVI. Research should focus on assessing the probability of having the disease using different approaches to determine which performs better [7-9,16,24,25].

iii) **Investigation of artificial intelligence and machine learning techniques:** Their use, in the context of analyzing the expiratory flow/volume loop may offer improved precision in evaluating small airway function. Further research should investigate the potential of these techniques in improving the diagnosis and understanding of OVI [3,37].

By pursuing these future steps, it is possible to enhance the understanding and diagnosis of OVI, leading to improved patient care and outcomes.

Conclusion

In conclusion, the standardization of the OVI definition is a complex issue that requires a balance between population-based approaches and individual patient perspectives [38]. The selection of an appropriate definition should prioritize the benefit to the patient in terms of early disease management, while avoiding overdiagnosis and unnecessary costs. It is recommended that scientific organizations and professional societies revisit evidence-based medicine principles, revise their guidelines, and work towards proposing a standardized definition for OVI. By doing so, healthcare professionals can ensure consistent and effective diagnosis and management of OVI, ultimately improving patient care and outcomes.

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Conflicting Interest

None.

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