

An approach to interpreting restrictive spirometric pattern results in occupational settings

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KEY WORDS

Diagnostic algorithm; FEV₁; FVC; FEV₆; FEV₁/FVC; interpretative criteria; lung function testing; occupational exposure

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Algoritmi diagnostici; FEV₁; FVC; FEV₆; FEV₁/FVC; criteri interpretativi; test di funzionalità polmonare; esposizione occupazionale

SUMMARY

Objectives: *The aim of this review is to provide an updated overview of definition, epidemiology, diagnostic algorithm and occupational exposures related to abnormal restrictive spirometric pattern (RSP) in order to improve the correct interpretation of spirometry test results by occupational healthcare providers.* **Methods:** *A review of the scientific English literature of the last 25 years was carried out with MEDLINE and related keywords [(restricti* AND spirometr*) AND occupational]. The first step analysis covered 40 studies and the second step the reference list. Results are presented in four major aims and subquestions.* **Results:** *A spirometric pattern of reduced VC (Vital Capacity), together with a normal FEV₁ (Forced Expiratory Volume in 1 Second)/VC ratio, is suggestive, though not diagnostic of restrictive ventilatory defect (RVD). The prevalence of RSP is high in some studies, comparable to obstructive pattern, and could be associated to chronic medical conditions (diabetes, congestive heart failure, obesity, hypertension) as well as to increased risk of mortality and lung cancer. In order to predict true restrictive defect [TLC-(Total Lung Capacity) < LLN (Lower Limit of Normality) gold-standard for diagnosing restrictive lung diseases (RLD)] from spirometric data, mathematical models have been developed, but more studies in occupational setting are necessary to clarify the accuracy of such approaches in health surveillance programmes. Occupational exposures that may lead to restrictive impairments are inhaled inorganic dusts (silica, asbestos), organic dusts (mainly from hypersensitivity pneumonitis agents) and other inhaled agents (synthetic fibers and flavorings).* **Conclusions:** *For spirometric data reliability it is mandatory to perform appropriate pulmonary function tests and use updated interpretive criteria. A reliable interpretation permits early recognition of RSP and, when indicated, to report workers to second level exams (TLC, decreased diffusing capacity for carbon monoxide [DLco], chest imaging). The application of mathematical models to better predict a reduction in TLC from spirometric data in occupational settings is required in order to reduce excessive costs and useless exams in health surveillance programmes.*

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RIASSUNTO

«*Approccio interpretativo del pattern restrittivo spirometrico in ambito occupazionale*». **Obiettivi:** Scopo di questa revisione è fornire un aggiornamento sulla definizione, epidemiologia, algoritmi diagnostici ed esposizioni occupazionali correlati a pattern spirometrici anomali di tipo restrittivo (RSP) al fine di migliorare la corretta interpretazione dei risultati spirometrici. **Metodi:** È stata condotta con MEDLINE una revisione della letteratura in lingua inglese degli ultimi 25 anni con le seguenti parole chiave [(restricti* AND spirometr*) AND occupational]. Il primo step è stata la valutazione di 40 articoli che trattano di tecniche spirometriche, dell'uso di modelli matematici sui dati spirometrici per prevedere meglio una riduzione della capacità polmonare totale (TLC), e su studi di prevalenza di anomalie della funzione polmonare in vari ambiti lavorativi. Il secondo step è stata la valutazione degli articoli in bibliografia. I risultati sono sintetizzati in 4 obiettivi principali e alcuni secondari. **Risultati:** Una riduzione della capacità vitale (VC) alla spirometria, associata ad un normale rapporto FEV_1 (Forced expiratory volume in 1st second)/VC, è suggestiva ma non diagnostica di un deficit ventilatorio restrittivo (RVD). La prevalenza di RSP è alta in alcuni studi, paragonabile al pattern ostruttivo, e potrebbe essere associata a condizioni croniche (diabete, insufficienza cardiaca congestizia, obesità, ipertensione), nonché ad aumento di mortalità e di incidenza di cancro polmonare. Diversi modelli matematici sono stati introdotti per predire un deficit restrittivo [TLC-(Total Lung Capacity) <LLN (Lower Limit of Normality) gold standard per la diagnosi di patologie polmonari restrittive] dai dati spirometrici, ma ad oggi sono auspicabili più studi per chiarire meglio l'accuratezza di questi approcci in ambito di sorveglianza sanitaria. Esposizioni professionali a polveri inorganiche (silice, amianto), polveri organiche (principalmente agenti di polmonite da ipersensibilità) ed altri agenti (fibre sintetiche e aromi) possono determinare RSP. **Conclusioni:** Perché la diagnosi sia attendibile è necessario eseguire test di funzionalità polmonare appropriati utilizzando criteri interpretativi aggiornati. Un'interpretazione affidabile permette di riconoscere precocemente RSP ed indirizzare i lavoratori a esami di secondo livello (TLC, DLco, imaging). L'applicazione di modelli matematici per prevedere una riduzione della TLC dai dati spirometrici è auspicabile in ambito occupazionale nei programmi di sorveglianza sanitaria per ridurre costi ed esami inutili.

INTRODUCTION

In occupational setting, spirometry is a basic tool for respiratory health surveillance. It can be safely performed on-site at low cost and allows demonstration of a specific pattern of respiratory impairment. Test quality remains the most important concern in lung-function testing. It is an effort-dependent test that requires careful instruction and the full cooperation of the patient. The inability to perform acceptable and repeatable manouvres may be due to poor subject motivation, poor coaching techniques or failure to understand instructions (3). Other fundamental elements that lead to high quality test results are accurate equipment, an ongoing program of quality control, appropriate reference values and good algorithms for results' interpretation (15). Results of spirometry tests are critically important in the occupational setting when used for screening and surveillance programmes (70). Poor quality test

increases the misclassification rates for obstructive and nonobstructive pattern and the subsequent results of occupational and environmental surveillance.

Airflow obstruction is diagnosed with high reliability and validity using the American Thoracic Society and European Respiratory Society (ATS/ERS) recommendations for spirometry (7, 72). Obstructive pattern is defined as the disproportionate reduction in the forced expiratory volume in the first second (FEV_1) relative to vital capacity (VC) leading to an abnormal FEV_1/VC ratio.

However, large epidemiological studies (13, 55, 60, 98) revealed that a substantial proportion of population, far more than what would be expected as a result of interstitial lung disease, has nonobstructive abnormal spirometry results.

The most widely accepted term to define nonobstructive spirometry is restrictive spirometry pattern (RSP) or restrictive ventilatory defect (RVD) or restrictive impairment. Some occupational healthcare

providers may be unfamiliar with these terms and definitions, and this pattern needs a careful description.

This paper provides an overview of the definition of nonobstructive spirometric pattern and RSP, with a focus on severe restrictive impairment; moreover, it describes epidemiological and clinical outcomes related to RSP. The aim of this review is to provide, in occupational perspectives, diagnostic algorithm to predict reduced TLC (Total Lung Capacity) from abnormal spirometric data [comprising the use of FEV₆ (Forced Expiratory Volume in 6 second) as surrogate of FVC (Forced Vital Capacity)] and a partial list of known causative agents. This review is intended to improve the correct use and interpretation of spirometry test results in occupational healthcare.

METHODS

Original articles and reviews on spirometric interpretative strategies for restrictive impairment with occupational perspectives were reviewed for the period 1990 to 2016 inclusive. These dates were chosen because we wanted to focus on the literature over the past decades. Searches were made with search engines (MEDLINE and Thomson Reuter Web of Science) and related keywords [(restricti* AND spirometr*) AND occupational]. A review of English scientific literature was carried out focusing on those papers dealing with spirometric techniques, occupational studies on prevalence of lung function impairments and use of mathematical models to better predict a TLC reduction from spirometric data.

RESULTS

Searches with engines were made with related keywords [(restricti* AND spirometr*) AND occupational] in all fields and in title with time as filter (publication period 1996–2016) and species filter (human). Results were further filtered for English language and the new searches produced 101 papers. Papers dealing with obstructive impairment

[asthma or chronic obstructive pulmonary diseases (COPD)] as well as infectious diseases, lung cancer and paediatric respiratory or cardiac impairments were excluded; 40 articles were then selected and, subsequently, all quoted references were evaluated for the scope of the review. The results are summarised in 4 major aims and subquestions:

- 1 Definition of nonobstructive spirometric pattern
 - Severity of restrictive impairment
- 2 Epidemiology
 - Outcome related to RSP
- 3 Mathematical model to predict reduced TLC from spirometric data and occupational perspectives
 - FEV₆ as surrogate for FVC in detecting restriction
- 4 Occupational exposures associated with RSP

Definition of nonobstructive spirometric pattern

Many terms have been used to describe different entities included in nonobstructive spirometric patterns, defined as a preserved FEV₁/VC ratio due to deficits in FEV₁ and/or VC (Figure 1). Preserved Ratio Impaired Spirometry (PRISm) (102), which has alternatively been defined also as “GOLD-(Global Initiative for Chronic Obstructive Lung Disease) unclassified” (101,105) is characterized by a preserved FEV₁/VC ratio with low FEV₁ only. Another term present in literature is “non-specific” pattern (31, 32) characterized by reduced FEV₁ and VC, a normal FEV₁/VC ratio, and a normal total lung capacity (TLC), named, by some authors, small airway obstruction syndrome (SAOS) (87). This phenotype, according to ATS/ERS Task Force, is due to the subject failing to inhale or exhale completely (poor effort) and labeled as representing obstruction. Hyatt and co-workers attributed these frequent patterns (10–15% of adult) to “volume loss” perhaps due to “volume derecruitment” secondary to obesity (a zero expiratory reserve volume), premature termination of FVC maneuver (causing a falsely low FVC), or airway closure of small airways during forced exhalation (not measured by FEV₁/

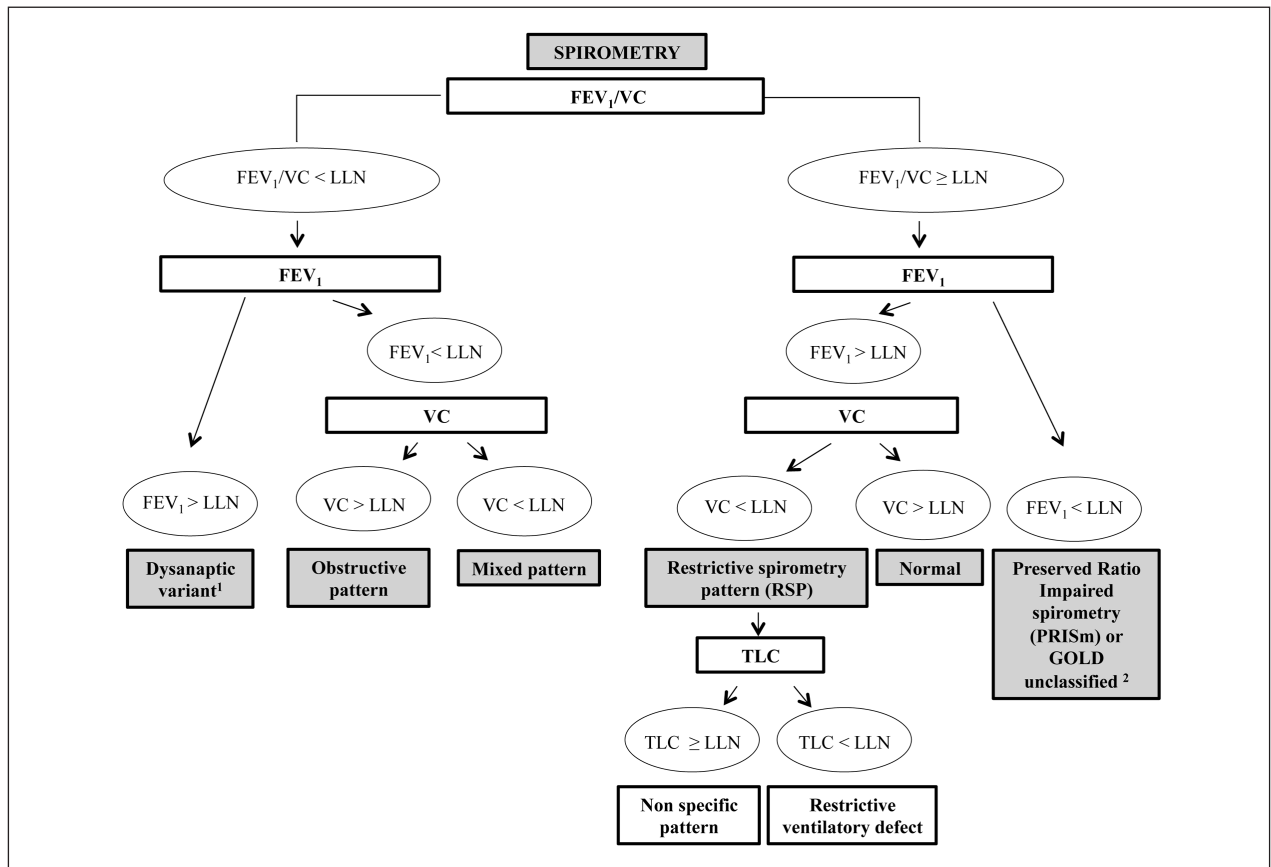


Figure 1 - Algorithm for the diagnosis of obstructive and non obstructive pattern.

Figure legend: FEV₁: forced expiratory volume in 1st second; VC: vital capacity; LLN: lower limit of normality; TLC: total lung capacity; COPD: chronic obstructive pulmonary diseases; ¹(Pellegrino R et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005 [72]); ²(Wan ES et al. Investigators. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISM) in COPD. *Gene. Respir Res.* 2014 [102] and Wan ES et al. Clinical and radiographic predictors of GOLD-unclassified smokers in the COPD Gene study. *Am J Respir Crit Care Med.* 2011 [101]).

FVC) (32). This appears to be a distinct and stable pulmonary function test pattern with roughly two-thirds of patients continuing to show this result on follow-up testing (36). Many patients exposed to fumes, dust, and gases at Ground Zero (after the World Trade Center attacks) who had asthma-like symptoms (suggesting reactive airway dysfunction), showed a “spirometric restriction” with a normal FEV₁/VC (86). Some of them, had abnormally high airway resistance measured using forced oscillation tests (16, 85).

The most widely accepted term to define nonobstructive spirometry is restrictive spirometry pattern (RSP) or restrictive ventilatory defect (RVD) or restrictive impairment. These terms are not the same

concept of restrictive lung disease (RLD) and performing a spirometry may conduct to the suspicion of restrictive ventilatory defect (RVD) or restrictive spirometry pattern (RSP), but not leading to the diagnosis of restrictive lung disease (RLD) (71).

Indeed RVD includes (table 1):

- Intrinsic lung diseases, which cause inflammation or scarring of the lung tissue (interstitial lung disease) or fill the airspaces with exudate or debris (acute pneumonitis) that could be considered the real RLD. Therefore, the term RLD refers to a decrease in total lung volume due to impaired expansion from decreased lung elasticity, or to loss of lung tissue (pneumonectomy or mass). It is diagnosed using volume measurements (total lung capacity, TLC);

Table 1 - Partial list of Restrictive Ventilatory Defects

Types of restrictive ventilatory defects	Example
Intrinsic lung diseases (Restrictive Lung Diseases)	
Interstitial lung diseases (ILD)	Associated with diseases (rheumatic diseases, vasculitides, hemorrhagic syndromes, amyloidosis, respiratory bronchiolitis, alveolar proteinosis, etc.), exposures (inhaled inorganic dust, organic dust, fumes and vapors see table 3), drugs (antibiotics, anti-inflammatory, chemotherapeutic agents, anti-arrhythmic agents, illicit drugs) Idiopathic condition (sarcoidosis, cryptogenic organizing pneumonia, acute and chronic eosinophilic pneumonia), and the idiopathic interstitial pneumonias further characterized in: idiopathic pulmonary fibrosis (usual interstitial pneumonia), desquamative interstitial pneumonia, respiratory bronchiolitis-interstitial lung disease, acute interstitial pneumonia, and nonspecific interstitial pneumonia Interstitial Pulmonary fibrosis
Acute pneumonitis	Alveolar Pneumonia. Acute respiratory distress syndrome. Interstitial pneumonitis
Loss of lung tissue	Pneumonectomy. Mass
Extrinsic disorders	
Pleural diseases	Effusion. Pleural thickening or scarring
Thoracic cage abnormalities	Scoliosis. Other Tumours or space-occupying lesions
Neuromuscular disorders	Myasthenia gravis. Spinal cord injury. Guillain-Barre´ syndrome

- Extrinsic disorders, such as disorders of the chest wall or the pleura, which mechanically compress the lungs or limit their expansion;

- Neuromuscular disorders, which decrease the ability of the respiratory muscles to inflate and deflate the lungs.

The clinical history (dyspnoea and decreased exercise capacity are typical manifestations of restrictive impairment), physical examination, and chest radiograph are usually helpful in distinguishing among these disorders. Spirometry can be useful in suspecting restriction of lung volumes. Evaluation of lung volumes and diffusing capacity are helpful in confirming the presence of restriction and assessing severity of impairment (11, 61).

According to the ERS statement, restriction is defined as a reduction of total lung capacity (TLC) below the 5th percentile of the predicted value (=LLN) with a normal FEV₁/FVC ratio. This implies measuring lung volumes by plethysmography or dilution of inert gas (72). Both methods are expensive and time-consuming, and not easily applied

to large population-based epidemiological studies or to occupational settings. In these situations, when TLC measurements are unavailable, spirometry volume measures are used to suspect a restrictive pattern. Moreover, in nonresearch setting as in workplace, spirometry testing usually does not include VC measures, so that forced vital capacity (FVC) is used instead. Among occupational healthcare providers, there are two mostly used interpretative methods for establishing spirometrical restrictive pattern (GOLD cut-off and ATS/ERS LLN criteria). Regarding obstructive pattern, in 2001 GOLD document provided a simple cut-off method (27): FEV₁/FVC ratio ≥ 0.7 , with a reduced FVC < 80% predicted and FEV₁ normal or mildly reduced. The GOLD-based thresholds assume incorrectly the equivalence of spirometric variability during lifetime, not considering that aging increases variability in spirometric performance. Infact, aging (starting at age 40) is associated with physiological lung changes, including decreased chest wall compliance, respiratory muscle strength, and lung performance,

affecting FEV₁, FVC, and FEV₁/FVC (37, 88, 99). Differently, ERS stated that “in the absence of airways obstruction (FEV₁/FVC ≥ LLN) the presence of a restrictive impairment may be suspected with spirometry when VC is reduced (<LLN) and the flow-volume curve shows a convex expiratory pattern”. LLN represents the lower 5th percentile of the predicted value accounting for a person’s age, height, sex, and race/ethnicity.

Severity of restrictive impairment

A decline in VC has been recognized to be correlated with loss of lung compliance, a sensitive measure of impairment in interstitial diseases (8, 11, 36). In 1991, ATS guidelines recommended categorization of the severity of obstructive and restrictive defects based upon the degree of reduction in FEV₁ and VC, respectively (4). Differently, in 2005 ERS reported: “Grading of restrictive impairment is on the basis of the FEV₁% of predicted. This may be reasonable since both the FVC and FEV₁ are reduced as restrictive impairment progresses, and the common technical problems of early termination of maneuvers and zero-flow errors are less likely to impair the accuracy of the FEV₁ than the FVC” (72). ERS suggested using FEV₁ in categorization of both obstructive and restrictive defects because of its simplicity compared to ATS method. The rationale for such a proposal, in disorders presenting with restrictive defects, is because the FEV₁/VC ratio is preserved (normal or increased) and hence there may be a good correlation between reduction in VC and the corresponding reduction in FEV₁. The categorization was the following: mild (FEV₁% pred ≥ 70), moderate (FEV₁% < 69 and ≥ 60), moderately severe (FEV₁% < 59 and ≥ 50), severe (FEV₁% < 49 and ≥ 35), very severe (FEV₁% < 35).

However, there is a scientific debate (65) to decide whether is more useful to grade severity based on FVC, which is a volume-related parameter, or on FEV₁, as suggested by ERS. FEV₁ is probably better when applied at epidemiological level because of its reproducibility, its robustness; in addition, FEV₁ is more suitable to assess longitudinal changes in lung function due to obstructive or restrictive im-

pairment (33). Moreover, it is helpful in nonspecific pattern or patients with mixed disease in absence of lung volumes, when the contribution of restriction and obstruction is unknown (65). For workers with mixed patterns, grading the restrictive impairment using FEV₁% of predicted might slightly overstate the severity of restriction due to the coexisting obstructive reduction of the FEV₁ (70). However, as demonstrated in an Indian study of Aggarwal et al. (2), there was more than 40% discordance between data severity defined by the two methods of categorization, with a tendency versus an underestimation of the severity of airway restriction as compared with the old ATS guidelines. This could be explained by the fact that, in several patients with restrictive defects, FEV₁/FVC ratio is increased, thus the reduction in FVC is relatively greater than corresponding reduction in FEV₁. Furthermore, for patients with a diagnosis of RLD, serial spirometry can be useful to assess progressive changes in FVC, that may be related to disease progression or response to treatment; this approach has been used as a primary endpoint in regulatory efficacy trials (41).

Epidemiology

The prevalence of restriction on spirometric data is high in some studies, even comparable to the prevalence of obstructive pattern, albeit its assessment is problematic because of changing definitions and measurements not specifically obtained after bronchodilator inhalation, because the use of populations in different ages (84), different predictive equations and classifications of disease (28, 89). Burden of Obstructive Lung Disease (BOLD) studies have shown a striking geographic variance (13). Interestingly, this research found a powerful correlation between presence of restriction and poverty. Worldwide prevalence in 2012 was found to be 11.7% for men and 16.4% for women (considering restriction as FVC < LLN) (60).

Analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) found that 6.6% of patients showed restrictive lung abnormalities (defined as FEV₁/FVC ≥ LLN and FVC < 80% pred) (55). Moreover, the

prevalence varied depending on ethnicity: among white Americans, African Americans and Mexican Americans, it was 5.6% (4.6% to 6.5%), 8.0% (6.9% to 9.0%) and 5.7% (4.5% to 6.9%), respectively (98). In a study of Kurth et al. (45), the prevalence of restrictive pattern was re-analyzed in NHANES III population in two sampling periods (1988-1994 and 2007-2010) using ATS/ERS LLN criteria instead of GOLD cut-off (55). Age-standardized prevalence decreased significantly from 7.2% (1988-1994) to 5.4% (2007-2010). Factors positively associated with restrictive pattern on spirometry included age, female gender, white race, lower education, former and current smoking, and comorbidities including doctor-diagnosed cardiovascular disease, doctor-diagnosed diabetes, and abdominal obesity.

In addition, adopting different spirometric prediction equations lead to different diagnostic and interpretative consequences and to various prevalence of spirometric abnormalities. Specifically, GLI (Global Lung Initiative) 2012 equations increase the prevalence of a "restrictive spirometric pattern" ($FEV_1/FVC > LLN$ and $FVC < LLN$) compared to The European Coal and Steel Community (ECSC), but decrease it compared to NHANES (74).

Outcome related to RSP

The clinical relevance of a spirometrically-defined restrictive ventilatory defect is uncertain in the absence of respiratory symptoms, signs of pulmonary fibrosis, or other assessments (82). Studies have provided evidence supporting the association between chronic medical conditions and restrictive spirometric results including diabetes (18, 22, 47), congestive heart failure (CHF) (12, 21, 34, 38), obesity (52) and systemic hypertension (58). The relationship between hypertension and restrictive lung disease is difficult to determine since many of the aforementioned factors (obesity, CHF and diabetes) are also associated with hypertension. Another potential factor for the presence of restriction on spirometry is, somewhat ironically, the presence of a diagnosis of asthma or COPD. In one study of asthma patients, 24% met criteria for restriction

(64). In a report of patients with a clinical diagnosis of COPD, 14% had also restriction on spirometry (42). This raises the possibility that restriction might either represents a phenotype of obstructive diseases or results from the development of complications of obstructive diseases. Nonetheless, a third possibility is the misclassification of restrictive pattern.

Analyses have also shown increased mortality in patients with this abnormality; several studies have reported, in patients with restriction on spirometry, an increased risk of mortality (55, 56, 58, 59), future insulin resistance (18, 22, 25, 47), incident lung cancer (57, 73) and systemic inflammation (54, 63).

Mathematical models to predict reduced TLC from spirometrical data

The question that arises is whether spirometry has good accuracy to predict reduced TLC and restrictive lung disease. In recent years, different studies evaluating the use of spirometry in the diagnosis of restrictive lung impairment have been performed using spirometric data derived and validated in different setting (table 2).

In 1991, the American Thoracic Society defined the restrictive pattern as reduced TLC; however, the presence of a restrictive pattern could be derived from a normal FEV_1/FVC ratio with a reduction in VC (4).

In 1994, Crapo (15) suggested that a restrictive pattern may be cautiously diagnosed from the spirometric examination with low spirometric FVC together with a normal or high FEV_1/FVC ratio in absence of moderate-to-severe airflow obstruction. The definitive finding for a restrictive pattern is a reduced TLC, even though VC has frequently been demonstrated to be more useful in following the course of restrictive lung diseases (41).

However, since 1999, studies verifying the accuracy of this interpretation and the accuracy of spirometry at ruling out restrictive impairment were lacking. Different mathematical models have also been described to help the prediction of TLC reduction from spirometric data, but the accuracy of such approaches either in individual patient or in occupational setting is not clearly known.

Table 2 - Comparison of diagnostic algorithms present in the literature

Author, year and reference	Patients	Theoretical set	Algorithm	Performance for predicting a reduced TLC
Aaron et al 1999 [1]	1831 Caucasians (49.8% M mean age: 50.8±17.6)	- Spirometry: Enright if ≥65yrs; Knudson if <65yrs - TLC: Crapo	TLC <LLN gold standard vs FVC <LLN and FEV ₁ /FVC ≥LLN	FVC <LLN Sn:86%; Sp:83%; PPV:41%; NPV 97.6%. FVC <LLN and FEV ₁ /FVC ≥LLN Sn:68%; Sp:93%; PPV:58%; NPV:95.4%.
Glady et al. 2003 [26]	Caucasians in two groups: 259 for derivation (53.3% M mean age: 52.8±16.2) and 265 caucasian (55.5% M mean age: 54.2±15.6) for validation of algorithm	- Spirometry: Crapo or Morris - TLC: Crapo or Goldman and Becklake	FVC <85% pred and FEV ₁ /FVC≥55%	Sn:96%; Sp:61%; PPV:40%; NPV:98%.
Swanney et al. 2004 [91]	219	- Spirometry: NHANES III - TLC: Crapo or Goldman and Becklake	FVC < 102% of the LLN FEV ₁ /FVC ≥63% and FEV ₆ < 106% and FEV ₁ /FEV ₆ ≥ 68%	FVC (best results with Goldman and Becklake reference values) Sn:97%; Sp:81%; PPV:49%; NPV:99%. FEV ₆ Sn:97%; Sp:76%; PPV:42%; NPV:99%.
Venkateshiah et al. 2008 [100]	8315 (52% M, 86% caucasians, 14% African-Americans; 57±14 yr)	- Spirometry: NHANES III - TLC: Crapo	FVC<LLN compared to FVC <LLN and FEV ₁ /FVC >LLN	FVC <LLN Sn:88.6%; Sp:56.8%; PPV:39.9%; NPV 93.9%. FVC<LLN and FEV ₁ /FVC>LLN Sn:72.4%; Sp:87.1%; PPV:64.4%; NPV:90.7%.
Khalid et al. 2011 [40]	Caucasians and afro-americans into two groups: 473 for derivation and 517 for validation	- Spirometry: NHANES III - TLC: Crapo	[(FEV ₁ /FVC)% pred/ FVC % pred] of 1.11 (=0.78/0.70)	Sn:95%; Sp:44%; PPV:22%; NPV:98%.
Mehrpavar et al. 2014 [62]	1224 Iranians (708 restrictive and 516 without restriction)	- Spirometry: Golshan et al - TLC: Golshan et al	FVC<LLN + FEV ₁ /FVC ≥ LLN	Sn:98.7%; Sp:78%; PPV:77.3%; NPV:98.8%.

(continued)

Table 2 (continued) - Comparison of diagnostic algorithms present in the literature

Author, year and reference	Patients	Theoretical set	Algorithm	Performance for predicting a reduced TLC
De Matteis et al. 2016 [20]	186 Caucasians (50% M median age: 46) for derivation data set and 190 caucasian <65 years (not specified gender and median age for validation)	- Spirometry: Crapo and Hankinson - TLC: Crapo	FVC <70% pred and FEV ₁ /FVC ≥70%	FVC <70% pred + FEV ₁ /FVC ≥ 70% Sn:71%; Sp:96%; PPV:67% and 15% (for prevalence of 10 or 1% respectively); NPV 97% and 100% (for prevalence of 10 or 1% respectively).

Legend: Sn (sensitivity), Sp (specificity), PPV (positive predictive value), NPV (negative predictive value)

In 1999, Aaron et al. (1) on the basis of a retrospective study on 1831 adult patients, suggested that anormal FVC led to a negative predictive value (NPV) of 97.6% for restriction based on lung volume measurements and the combination of low FVC with normal FEV₁/FVC led to a positive predictive value (PPV) of 58% compared to a "gold standard" of lung volume measurements. This means that, for typical restrictive spirometrical pattern (FVC<LLN and FEV₁/FVC≥LLN), only 58% of patients were found to have true lung volume restriction.

In 2003, Glady et al (26) developed a spirometry-based algorithm to predict restrictive pulmonary impairment in Caucasian subjects. The algorithm had a high sensitivity (96%) for predicting restriction and a high NPV (98%) for excluding restriction, but could not predict a low TLC. According to their algorithm, only patients with FVC<85% of predicted and FEV₁/FVC≥55% required lung volume measurements after spirometry.

In 2004, Swanney et al (91) in a retrospective study of 219 patients compared the performance of three spirometric algorithms (ATS, Glady and their proposed FEV₆<106% of the LLN and FEV₁/FEV₆ ratio≥68%) and confirmed previous study that spirometric patterns could not reliably predict a reduced TLC, but could reliably predict a TLC≥normal level. Moreover, the NPV was not affected by the reference values and substituting FEV₆ for FVC (more

reproducible and less physically demanding) led to equivalent outcomes.

In 2004, Boros et al. (10) analyzed spirometric and lung volume measurements from a sample of 1173 patients with an established or tentative diagnosis of interstitial lung disease without airflow obstruction. Measurements of VC was not reliable for detecting restrictive changes because the sensitivity was only 69.3%, NPV was 91.5% (which means that a normal VC did not exclude the possibility of restriction in 8.5% of patients with true restriction). This suggests that the proposed algorithm based on FVC>LLN to curtail lung volume measurements may depend on the suspected diagnosis or severity of lung disease.

In 2008, Venkateshiah et al. (100) in a retrospective study tried to assess the utility of spirometry to diagnose or to exclude pulmonary restriction comparing spirometric data with lung volume measurements of 8315 patients. They concluded that the NPV for a normal FVC (defined as ≥LLN using the NHANES III) is up to 95.7% for excluding restriction, and that a spirometric diagnosis of restriction (FVC<LLN and FEV₁/FVC>LLN) had a PPV up to 73.9%. Analysis of ROC curves confirmed that spirometry more reliably excluded restriction when the criterion FVC<LLN was used than when the combine criteria of FVC<LLN and FEV₁/FVC≥LLN were used.

In 2011, Khalid et al. (40) created a distinct algorithm tested in patients whose spirometry show both obstruction and a low FVC to better predict the absence of restriction. The highest association with TLC was a value of 1.11 of this algorithm [(FEV₁/FVC) % predicted/FVC % predicted]. The performance was better than prior published algorithms with a sensitivity, specificity, positive predictive value and negative predictive value of 95%, 44%, 22%, and 98%, respectively.

In 2014, Mehrparavar et al. (62) evaluated the diagnostic accuracy of spirometry for detection of restrictive lung pattern in occupational setting using two criteria: FVC<LLN alone and along with FEV₁/FVC>LLN. The results were compared to lung volume measures; the second criterion was more accurate than the first, with sensitivity, specificity, PPV and NPV of 98.68%, 78%, 77.3% and 98.83%, respectively.

A recent paper of De Matteis et al. (20) proposed a new spirometry-based algorithm to predict pulmonary restrictive impairment in occupational health setting with an expected *a priori* low prevalence of restrictive lung disease (at most 1-10%). Their best algorithm (FVC<70% predicted and FEV₁/FVC≥70%) has 96% of specificity and PPV ranging from 67 to 15% for a disease prevalence of 10 and 1%, with the lowest proportion of false positive (4%) and high sensitivity (71%) in comparison with other previous algorithms.

FEV₆ as surrogate of FVC in detecting lung restriction

Previous studies have demonstrated that FEV₆ can be a reliable surrogate of FVC in the detection of obstruction as well as in the exclusion of restriction (90, 91, 95, 96). Swanney et al. (91) demonstrated that FEV₆ is equivalent to FVC in the detection of a reduced TLC by testing whether it made any difference if FVC or VC were replaced by FEV₆ in three different spirometry-based algorithms for predicting a reduced TLC. For instance, the ATS algorithm was used to compare the performance of the combined condition (FEV₁/VC≥LLN and FVC<LLN) versus the combined condition (FEV₁/

FEV₆≥LNN and FEV₆<LLN), against the gold standard (TLC<LLN). This yielded a PPV of 55% for both and a negative predictive value (NPV) of 99% for both. Akpınar-Elci et al. (3) compared the “gold standard” definitions of spirometry restrictive impairment (FVC below the LLN with a normal FEV₁/FVC %) with definitions based on FEV₆ (FEV₆ below the LLN with a normal FEV₁/FEV₆). They demonstrated that a significantly high overall agreement was obtained between the two definitions, confirming that FEV₆ can be used as a surrogate for FVC in workers, although with some misclassification when compared to obtaining ATS-acceptable manoeuvres of longer duration. Vandevoorde et al. (97) confirmed the assumption that FEV₆ is equivalent to FVC in the detection of a reduced TLC and proposed a sex-dependent algorithm to identify patient groups for whom a reduced total lung capacity can be either positively detected or ruled out solely by use of a FEV₆ or FVC measurement. Restriction can be ruled out if FVC or FEV₆ is >100% pred (males) or >85% pred (females). In obstructive patients, spirometry can not reliably diagnose a concomitant restrictive defect, but it can rule out restriction for patients with FVC or FEV₆ >85% pred (males) or >70% pred (females).

Occupational exposures associated with RSP

In occupational settings, spirometry is important both to early diagnose occupational respiratory diseases in individual workers and for monitoring effects of exposure and maintaining effective preventive measures for the entire working population.

The most common inhaled pollutants which could induce restrictive impairments are: inhaled inorganic dusts (silica, asbestos), organic dusts [mainly from hypersensitivity pneumonitis (HP) agents], other inhaled agents (synthetic fibers and flavorings) (table 3). As shown in the literature, it is mandatory to early recognize RSP to address workers to pulmonary second level exams (TLC, DLco, chest imaging); functional parameters are also used to monitor loss of lung function over the years even in occupational scenarios of low exposure or for for-

Table 3 – Occupational and environmental causes of interstitial lung disease.

Modified from Crystal, RG. Interstitial lung disease. In: Wyngaarden, JB, Smith, LH, Jr, Bennett, JC, (Eds), Cecil Textbook of Medicine, 19th ed, WB Saunders Co, Philadelphia, 1992

Inhaled inorganic dusts*Silicates*

Silica (“silicosis”). Asbestos (“asbestosis”). Talc (hydrated Mg silicates; “talcosis”). Kaolin or “china clay” (hydrated aluminum silicate). Diatomaceous earth (Fuller’s earth, aluminum silicate with Fe and Mg). Nepheline (hard rock containing mixed silicates). Aluminum silicates (sericite, sillimanite, zeolite). Portland cement. Mica (principally K and Mg aluminum silicates)

*Beryllium (“berylliosis”)**Carbon*

Coal dust (“coal worker’s pneumoconiosis”). Graphite (“carbon pneumoconiosis”)

Metals

Tin (“stannosis”). Aluminum: Powdered aluminium; Bauxite (aluminum oxide). Hard metal dusts: Cadmium; Titanium oxide; Tungsten; Niobium; Cobalt; Vanadium carbides. Iron (“siderosis”, “arc welder’s lung”). Barium (powder of baryte or BaSO₄; “baritosis”). Antimony (oxides and alloys). Hematite (mixed dusts of iron oxide, silica and silicates; “siderosilicosis”). Mixed dusts of silver and iron oxide (“argyrosiderosis”). CuSO₄ neutralized with hydrated lime (Bordeaux mixture; “vineyard sprayer’s lung”). Rare earths (cerium, scandium, yttrium, lanthanum)

Inhaled organic dusts

Agents of hypersensitivity pneumonitis (such as Thermophilic fungi, Bacteria, Aspergillus, Cryptostroma corticale, Aureobasidium pullulans, Penicillium species, Animal proteins, etc)

Other inhaled agents*Chemical sources*

Synthetic - fiber lung (Orlon, polyesters, nylon, acrylic). Bakelite worker’s lung. Vinyl chloride, polyvinyl chloride powder

Gases

Oxygen. Oxides of nitrogen. Sulfur dioxide. Chlorine gas. Methyl isocyanate

Fumes

Oxides of zinc, copper, manganese, cadmium, iron, magnesium, nickel, selenium, tin, and antimony. Diphenylmethane diisocyanate. Trimellitic anhydride toxicity

Vapors

Hydrocarbons. Thermosetting resins (rubber tire workers). Toluene diisocyanate (TDI - asthmatic reactions prominent). Mercury

Aerosols

Oils. Fats. Pyrethrum (a natural insecticide)

mer exposed individuals (asbestos), and finally, to discover new hazardous exposures.

The classical association of silica exposure with restrictive lung disease (nodular silicosis and progressive massive fibrosis) has been clearly demonstrated, as well as the recognition of the occurrence of obstructive changes (14, 79, 80). It has been observed an increased prevalence of restrictive changes with increased International Labour Organization (ILO)

radiographic profusions, while a statistically significant increased risk of obstructive and mixed changes has been observed with progressive massive fibrosis (80). Worldwide researchers have reported conflicting results from studies on whether silica exposures are associated with a loss of pulmonary function in the absence of radiographic evidence of silicosis. Studies of granite workers in Singapore (67) and Sweden (53), of grinders in the agate dust industry

in India (76), of fire brick workers in China (50), and of gold miners in South Africa (35) have found an association between silica exposure levels above the allowable Occupational Safety and Health Administration (OSHA) exposure limits (set at 0.10 mg/m³, higher than NIOSH accepted level of 0.025 mg/m³) and pulmonary function loss in individuals without silicosis. In a study of automotive foundry workers in Midwest USA (30), authors found a 1.1-mL/yr loss in FEV₁ per mg per cubic meter of mean silica exposure and 1.6-mL decline in FVC per mg per cubic meter of mean silica exposure.

Health effects of occupational exposure to asbestos dust may be shown during the time of employment as well as many years after job termination. Very few surveys on longitudinal changes in pulmonary function in asbestos-cement workers are available (81, 83, 103). In a Polish study (92) on 3005 former workers who were employed in asbestos-cement production plant, further progression of spirometric parameters was assessed after termination of exposure to dust containing asbestos. RSP were registered in 21.6% of the patients, obstructive defects in 8.3%, whereas mixed changes in 7% (using GOLD cut-off method). Reduction of spirometric parameters (FEV₁, FVC, and FEV₁/FVC) was faster along with the increase of the number of cigarettes smoked per day. More rapid progression was also observed along with increasing termination of exposure. Having higher exposure was associated with a slower decline in FEV₁ and FEV₁/FVC ratios. A continuing controversy exists about whether asbestos exposure is associated with significant lung function impairments when major radiological abnormalities are lacking. In a systematic review and meta-analysis with data from 9,921 workers exposed to asbestos, Wilken et al (106) demonstrated a statistically significant reduction in VC, FEV₁ and FEV₁/VC, even in those workers without radiological changes, although the severity of the observed impairments is related to the degree of radiological abnormalities indicative of pleural fibrosis and asbestosis. The degree of lung function impairment was partly related to the proportion of smokers included in the studies. Another recent meta-analysis (43) estimated a summary effect of the decrements in percent predicted (% pred) FVC (4.09% pred,

95% CI 2.31 to 5.86) and FEV₁ (1.99% pred, 95% CI 0.22 to 3.77) associated with presence of pleural plaques among asbestos-exposed workers. Effects of similar magnitude were seen when stratifying by imaging type (X-ray or high-resolution CT). Undetected asbestosis was considered as an unlikely explanation of the observed decrements.

Exposure to agents causing HP may be associated to restrictive ventilatory defects associated with impaired gas exchange (DLco and/or hypoxemia on exercise) (75). Noteworthy, lung function parameters are normal in a substantial proportion (10% to 17%) of patients, particularly between episodes of acute HP (24, 29, 66). FEV₁/FVC ratio is often decreased in HP, suggesting some degree of airflow obstruction that has been related to bronchiolitis and emphysema. An obstructive or mixed pattern of ventilatory impairment has been described in 0.5% to 33% of patients in large series of HP (19, 23, 24, 29). In a paper by Nowicka et al. (69) the records of 111 patients (68 women) with a diagnosis of HP over a period of 18 years (1995-2013) were reviewed. Authors concluded that the diagnosis of HP at a young age is predictive of a more severe clinical course of disease, with lung fibrosis and higher disturbances in pulmonary function. Lung function was impaired more seriously in the youngest age group, with DLco <40% in 69.2% of these patients and restrictive pattern in 92.3%, as compared with the 41.0% in the whole cohort. Very few data are available on longitudinal decline of exposed workers (46, 107), but this is probably due to the suggested avoidance of occupational exposures in workers with HP as a gold standard for therapy.

Exposure-related spirometric abnormalities consistent with a restrictive process evolved during employment have been demonstrated in microwave popcorn and flavoring manufacturing industries associated with exposure to inhaled diacetyl (2,3-butanedione), a main ingredient of artificial butter flavorings. In a recent longitudinal study by Kreiss et al. (44) the adjusted prevalence of restriction was 3.7 times expected than US general population with an average yearly FEV₁ decline greater than in general population (115 vs. 30 ml/year). Employees with higher potential for flavorings exposure had 3.0 times and 2.4 times greater average annual declines

in FEV₁ (81.3 and 94.5 ml/year for non-smokers and ever smokers, respectively) and FVC (94.8 and 125.1 ml/year for non-smokers and ever smokers, respectively), and had 5.8 times higher odds of having excessive FEV₁ declines than employees with lower potential for exposure.

In 1991, Loughheed and colleagues (51) recognized a cluster of interstitial lung disease (ILD) cases in textile workers exposed to flocked nylon in Canada. Nylon flock-associated ILD, or flock worker's lung (FWL), is now a recognized occupational disease attributed to the inhalation of flocked nylon fragments. FWL has been reported in workers exposed to polyethylene (9), polypropylene (6), and rayon flock (5). It is characterized by progressive dyspnea and cough with or without sputum production, a restrictive pulmonary function deficit and reduction in DLco. Current understanding of the effects of exposure to nylon flock has largely been derived from case series and cross-sectional data (5, 6, 17, 39, 104). The long-term effects of nylon flock exposure have been investigated in a study of Turcotte et al. (93) in 39 flock-exposed workers (9 with and 30 without FWL). They found that even in the exposed workers without FWL the average decline in FEV₁ calculated using Spirometry Longitudinal Analysis (SPIROLA) software was 46 mL/y (range, -27 to 151 mL/y). The FEV₁ slope exceeded the limit of longitudinal decline (defined in SPIROLA as a within-person variation of 4% and reference slope of 40 mL/y) in 30% (9/30) and was >90 mL/y in 10% (3/30) of the studied population.

DISCUSSION

A pattern of reduced VC, along with a normal FEV₁/VC ratio, is suggestive, though not diagnostic of RVD. Spirometry alone may be useful to exclude RLD rather than to diagnose it because of higher negative than positive predictive value in the identification of lung restriction (PPV<60%) (1, 97). Although such a 'restrictive pattern' on spirometry will identify a true restrictive defect (TLC<LLN) in about half of such patients, occupational healthcare practitioner continue to use spirometry to describe and grade severity of restrictive patterns (because

lung volumes are not available) in order to evidence hazardous inhaled exposures, as well as the effect of preventive campaign. Mathematical models have also been described to better predict a reduction in TLC from spirometric data, but more studies in occupational setting are desirable in order to clarify the accuracy of such approach in surveillance programmes. The suggested interpretative approach is ATS/ERS LLN criteria (FEV₁/FVC>LLN and FVC<LLN) in order to accurately estimate the prevalence of restriction in an aging working population. The severity grade is evaluated using FEV₁% predicted, a more reproducible and robust parameter, even if FVC is still used to evaluate clinical course in ILD.

Moreover, as with other medical tests, pulmonary function tests (PFT) do not make a diagnosis by themselves, and a careful patient history, occupational exposure information in terms of type and procedure source of hazardous inhalational dusts, vapours or fumes, environmental concentrations, and use of personal protective equipment are required to establish the pre-test probability of lung disease.

The identification of RVD is complicated by several factors including variation in individual performance and the impact of confounding factors, particularly obesity (71) and the effects of cigarette smoking. So an index of obesity [BMI or abdominal circumference (33, 48)] should always be measured at the same time as standing height (which is required to determine predicted values for most lung function results).

Moreover, quality is a fundamental goal for all occupational interpretative strategies. For an accurate measurement of a restrictive ventilatory defect, it is fundamental to monitor the correct duration and intensity of forced spirometry at least of 6 sec in adults with the manoeuvre that should last until a plateau is achieved on the volume-time graph - the so-called end of test (EOT) criterion defined as a <20-mL change in volume during the final 2 s of the manoeuvre as well as fulfilling all standards and quality control set by expert guidelines such as the ATS/ERS consensus (72), Primary Care Respiratory Society UK (formerly General Practice Airways Group) (49) and American College of Occu-

pational and Environmental Medicine (ACOEM) statements (70). Failure to obtain FVC manoeuvres with acceptable EOT plateaus is relatively common in the occupational and primary care settings, in some cases due to time constraints, lack of adequate technician training or dedication (leading to poor coaching), poor motivation of the subjects to keep blowing out, a high prevalence of subjects with severe airway obstruction, or a faulty spirometer that prematurely terminates data collection. These short FVC manoeuvres cause underestimations of the true FVC, making a healthy subject's FVC more likely to fall below the LLN, a falsely positive result mimicking 'restriction.' At the same time, the FEV₁/FVC ratio is falsely increased, so that subjects with mild airway obstruction are more likely to have a falsely negative result. These short exhalation times should be detected in the interpretation of the results. A method proposed for reducing this misclassification rate is to utilise reference equations based on 6-s manoeuvres (FEV₆) (3).

Longitudinal follow-up of workers exposed to inhalants is suggested in order to detect excessive lung function decline (77,78). Assessment of decline is affected by several factors, including: technical quality and test variability; testing frequency and duration of follow-up; and definition of excessive decline. The primary measurement used to assess longitudinal change should be the FEV₁, as it is less affected by technical factors than the FVC (70, 72). The most practical thresholds for clinicians are based on a 15% loss of FEV₁ from baseline in an individual test results (percent predicted method: baseline FEV₁% pred minus current FEV₁% pred if $\geq 15\%$ excessive decline) as recommended by ACOEM (70) and NIOSH (94). Easy-to-use software is then available (such as SPIROLA), which can calculate a limit of longitudinal decline, based on spirometry quality and variability (68). These approaches are valuable to detect the impact of preventive measures in a specific work setting. However, for patients with a diagnosis of RLD, serial spirometry can be useful to assess progressive changes in FVC that may relate to disease progression (41).

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“Asbestos-related diseases and biological index of cumulative dose in shipyard workers (1996-2015)”

The authors reported an error that need to fully replace the data already published. The mistake is in Table 3 and the incorrect information may interfere with the results' interpretation, misleading the reader. The new table with corrections is presented below.

Tabella 3 - Carico polmonare di corpuscoli e fibre di amianto per patologia asbesto-correlata

Table 3 - *Asbestos bodies (AB) and asbestos fibres (AF) lung content by diseases*

Patologie	Concentrazione° AB (gr/tsp)				Concentrazione° AF (gr/tsp)			
	N MG	Range	RMG* (IC 95%)	p value	N MG	Range	RMG* (IC 95%)	p value
Tumori polmonari	43 40,8	1,1 6.200	1 (Riferimento)	-	51 2.440	120 54.000	1 (Riferimento)	-
Mesoteliomi maligni	53 89,3	0,9 8.900	2,2 (1,01-4,8)	0,048	60 6.110	850 256.000	2,5 (1,4-4,5)	0,003
Asbestosi	3 1.596	860 4.300	39,1 (4,1-374,4)	0,002	3 27.359	10.000 128.000	11,2 (1,8-71,8)	0,011

° Media Geometrica x 1.000

* Rapporto fra Medie Geometriche e intervallo di confidenza al 95%, ottenuti come antilog_{10} dei coefficienti della regressione lineare e dei limiti inferiori e superiori al 95% per mesoteliomi maligni e asbestosi. La regressione lineare è stata effettuata utilizzando come variabili dipendenti $\log_{10}(AB)$ e $\log_{10}(AF)$ e i soggetti con tumore polmonare come riferimento.