COPD Historical Evolution and Current Challenges

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Abstract:

Chronic obstructive pulmonary disease (COPD) is a prevalent, heterogeneous, progressive, yet treatable condition whose global burden remains substantial amid persistent diagnostic shortcomings. This report synthesises evidence regarding: (i) the historical evolution of COPD definitions—from the anatomoclinical constructs of emphysema and chronic bronchitis to the contemporary syndromic framework consolidated in the 2022 redefinition and integrated into GOLD 2023; (ii) ongoing diagnostic controversies surrounding spirometry (post-bronchodilator FEV_1/FVC), including the fixed ratio (0.70) versus lower limit of normal thresholds, technical and interpretative variability, patient effort dependence, reference equation selection, and its limited implementation in real-world practice; (iii) epidemiological patterns, highlighting the high prevalence among adults aged ≥40 years (approximately 10–13%) and striking underdiagnosis (around 87.5% globally), with frequent late diagnosis and notable overdiagnosis in primary care; (iv) the adjunctive, phenotype-oriented contribution of imaging (such as quantitative CT and functional MRI), which enhances disease characterisation without replacing spirometry or routinely guiding therapeutic decisions; (v) exacerbations as central determinants of clinical outcomes—accelerating lung function decline, impairing functional status and quality of life, and sharply increasing short-term cardiovascular risk; (vi) mortality and prognosis, wherein multidimensional indices (BODE family, ADO, CODEX, COTE) outperform FEV_1 alone but demonstrate only moderate predictive accuracy; and (vii) the current landscape of personalised medicine and biomarker research, which, despite extensive investigation, has yet to yield a robust and generalisable single biomarker for routine diagnosis, phenotyping, or prognostic use (beyond the limited applications of eosinophils, CRP, fibrinogen, and FeNO). Overall, the report provides a comprehensive overview of the main conceptual, diagnostic, and prognostic challenges that continue to shape COPD research and clinical management.

Keywords: COPD; diagnosis; spirometry; exacerbations; biomarkers; mortality; personalised medicine; omics.

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent, heterogeneous, progressive, preventable and treatable condition that impacts a significant portion (one in ten) of the global adult population [1–4]. This condition has emerged as the third leading cause of mortality worldwide [2,5,6].

Nevertheless, regardless of national income, **>70% of cases of COPD remain underdiagnosed** [7,8], and diagnosis is frequently **delayed by >10 years** [9], largely because spirometry (required for confirmation) is not routinely available in many clinical settings. Even when COPD is identified, frequent **exacerbations** and **elevated mortality** remain major challenges. Substantial **clinical, epidemiological and biological** uncertainties also persist, making **personalised** diagnosis and care difficult.

In these matters, various stakeholders, including international research expert groups and leading pulmonology scientific societies (such as the European Respiratory Society – ERS - and the American Thoracic Society – ATS), have been working to determine which **issues are most relevant and pressing in the field**. These initiatives have led to the developing of prioritised lists to guide research over the next decade [10–12].

To contextualise these priorities, this report offers a concise historical overview and an evidence-aligned synthesis. Unless otherwise noted, **figures are author-generated;** calculations are documented in an Appendix to facilitate independent appraisal.

This report summarises:

(1) **to trace** the historical evolution of COPD definitions underpinning contemporary concepts;
(2) **to examine** current diagnostic challenges around spirometry utilisation and thresholds;
(3) **to evaluate** current COPD prevalence, **underdiagnosis**, **misdiagnosis** and diagnostic delay;
(4) **to oversee** clinical classification and management aligned with recent guideline updates;
(5) **to appraise** the central role of exacerbations in outcomes and care pathways;
(6) **to analyse** the 'mortality challenge' and available prediction tools; and
(7) **to outline** the evolution of **personalised** medicine in COPD

2 Historical Evolution of COPD Terminology and Understanding

Several definitions of COPD have been proposed, and its conception has evolved since the **17th century**. The term **'chronic obstructive pulmonary disease'** was introduced in 1965 by Dr **William Briscoe**. COPD has **recently** been defined as a "*heterogeneous lung condition characterised by chronic respiratory symptoms (dyspnoea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction*" [1,13]. (Figure 1)

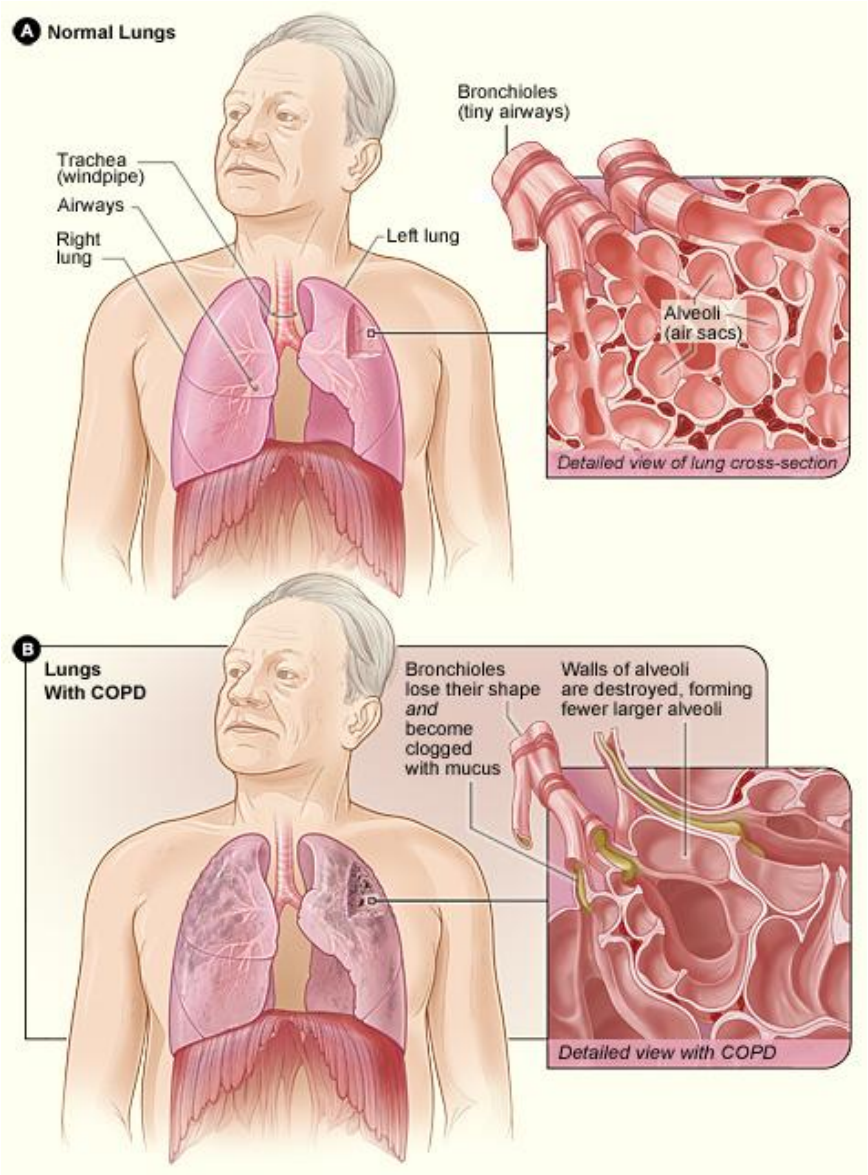

Figure 1. Comparison between normal lungs and COPD.
Public Domain [14]

2.1 COPD initial terms' origin: emphysema and chronic bronchitis.

The first written reports of this entity, which is now called COPD, can be reported as far as the old references and illustrations of **Ruysch's** *Observationum anatomico-chirurgicarum centuria.* (**1691**) about the presence of *vesiculis pulmonalibus obstructis* (obstructed pulmonary vesicles) in two patients suffering from a progressive respiratory limitation that ended with their death (Appendix 1). [15]

Nonetheless, some authors [16] indicated that, previously, Dr **Bonet** reported the presence of "***voluminous lungs***" in a patient with chronic dyspnoea, persistent cough and fever in his "*Sepulchretum sive anatomia practica ex cadaveribus morbo denatis*" (**1679**). This report could be one of the oldest available. The document related this clinical condition to a lung capillary coagulation that, in his opinion, was extended through the veins, provoking bronchial constipation and, consequently, insufficient air input in the lung (Appendix 2). [17]

Those cases would be defined by the term "**emphysema**", from the Greek ("ἐμφύσημα")' inflation, swelling', around the lungs' "inflated" or air-filled spaces reported. This term was introduced in 1819 by **Dr René Laennec** (1781–1826), creator of the (monaural) stethoscope (1815), in his dissertation "*De l'auscultation médiate*" (**1819**) [18,19]. This treatise was renamed and translated to English under the title "*A treatise on the diseases of the chest and on mediate auscultation*" (1827) and appointed one of the first "modern" definitions about and the relation with some relevant aspects:

> This [emphysema], next to hypertrophy, is the most simple of all the organic lesions of the lungs, since it consists simply in the dilatation of the air cells. **On this very account it remained long unknown, and has not hitherto been correctly described by any author.** I for a long time thought it very uncommon, because I had observed only a few cases of it; but since I have made use of the stethoscope, I have verified its existence as well on the living as the dead subject, and am led to consider it as by no means infrequent. I consider many cases of asthma, usually deemed nervous, as depending on this cause. The chief reason of this affection having been so completely overlooked is, that it is in some sort merely the exaggeration of the natural condition of the viscus.(*Laennec, 1819; Eng. transl. 1827, p. 148*) [20]

In his work, Laennec cites the Morbid Anatomy of **Dr Baillie** (1797) to establish **definitory elements of emphysema**; the lungs distended with air, the air cells of the lungs enlarged, and the air vesicles attached to the edge of the lungs [20,21]. He also describes several relative aspects that could be recognised nowadays as the presence of peripheral airway obstruction, collateral ventilation, loss of lung

recoil, right ventricular hypertrophy in its advanced disease form, all far in advance to their rediscovered centuries after [19].

However, the most remarkable part of this work is the relation that **Dr Laennec** established with "**catarrh**" as a cause of emphysema and a mutual contribution to his physiopathology. This relation, as a cause of emphysema, was more emphasised by Dr **Stokes** in his textbook "*Diagnosis and Treatment of Diseases of the Chest*" (1837) [22], extending this idea along the **British Empire**. This second component of COPD was previously described in 1814 by Dr **Badham** in "*An Essay on Bronchitis*" in his chapter about "**Chronic Cough**" and mucus hypersecretion [23]. This "**catarrh**" was renamed last to "**chronic bronchitis**" [19]. Both components constitute the core of COPD; nonetheless, the path to the current definition and diagnosis require another relevant element.

2.2 Spirometry creation and initial uses

In **1846**, based on the previous explorations of lung function, John **Hutchinson** developed and introduced the **spirometer** and his innovative concept of "***vital capacity***" (VC). This measurement, the *maximum air volume exhaled after full inspiration*, represented the first quantitative method to assess pulmonary function systematically. With this technique, Hutchinson **studied >2,000 men** and demonstrated it at the **Great Exhibition of 1851** (in the Crystal Palace). He envisioned spirometry as a diagnostic and prognostic tool of longevity, useful for insurances, a view **validated over a century later** by the **Framingham Study**. [19,24,25]

Although Hutchinson's spirometer was not used to investigate chronic bronchitis and emphysema during his day, his pioneering research laid the groundwork for respiratory diagnostics, facilitating the advancement of contemporary pulmonary medicine, and evolved slowly until the early 20th century. In **1908**, **Volhard** first observed a **slowed expiration in emphysema patients** [19].

In **1947**, Robert **Tiffeneau** and André **Pinelli** proposed the measurement of "**pulmonary capacity usable on exercise**" (*capacité pulmonaire utilisable à l'effort*) (**CPUE**), the maximal volume expelled in one second after a deep inspiration [26]. This CPUE term was renamed as "*volume expiratoire maximum seconde*" (**VEMS**) by a consortium of European pulmonologists convened in **Paris on 13 February 1954**, while the phrase "forced expiratory volume in a second (**FEV_1**)" was embraced by the **British Thoracic Society in 1957** [27].

In **1949**, Tiffeneau, Bousser and Drutel propose the utilisation of VEMS or FEV_1 **expressed as a percentage** of the *maximum breathing capacity* or *vital capacity* (currently named "*Forced vital capacity – **FVC***") as a **useful ratio for determining obstruction patterns** of the ventilation [28]. This ratio was proposed in parallel by **Gaensler** (1950), who named it "***Air Velocity Index (AVI)***". Gaensler also

identified it in different pulmonary diseases demonstrating that emphysema patients have a critical reduction with respect to healthy patients. For those calcs, measurements were previously adjusted ("**predicted**") considering **age and height** of the participants according to previous studies. This lower ratio limit of the normality in healthy participants in such studies were **76%** and **72%,** respectively. [29,28,30–32]

2.3 COPD origins (II): The combination of both terms

In 1958, the first "Aspen Emphysema Conference" introduced the concept of "**chronic bronchitis and emphysema syndrome (CB&E),**" recognizing the overlap between these conditions and proposing their classification under a unified framework [19,33,34].

Nonetheless, it is generally extended that was in the **CIBA Guest Symposium in 1959** [35] and the **American Thoracic Society (ATS) Committee on Diagnostic Standards in 1962** where the components of COPD were defined and the foundation for our definitions today [36].

CIBA maintains the **distinction between emphysema and chronic bronchitis**. While emphysema was defined as "*the condition of the lung characterized by an increase beyond the normal in the size of air spaces distal to the terminal bronchiole, either from dilatation or from destruction of their walls*," chronic bronchitis, described as "*the condition of subjects with chronic or recurrent excessive mucous secretion in the bronchial tree*," was categorized under the **omnibus term** "*chronic non-specific lung disease*". This latter term also encompassed "*generalized obstructive lung disease*," defined as a "*condition with widespread narrowing of the bronchial airways, at least on expiration, causing an increase above the normal in resistance to air flow*," which could either be reversible (such as in asthma) or irreversible [35].

Similarly, the **ATS** committee made the same definitions with **two major** differences, did not **consider a broad term** including asthma together with **chronic bronchitis**, and added **a temporal criterion** ("*present on most days for a minimum of 3 months in the year and for not less than 2 successive years* ") to the latter one. **Neither definition used any physiologic criteria**. Moreover, although the ATS committee recommended analysing spirometric values such as FEV1, FVC, and their ratios, it **did not provide any reference values.**

In **1965** by Dr William **Briscoe** in his article "*The slow space in chronic obstructive pulmonary disease*" was the first one to coin a new term "***chronic obstructive pulmonary disease***" for including **both emphysema and chronic bronchitis**, instead of the previous CB&E, and detailed description about its ventilation metrics. **This new term was progressively more extended** [37].

In **1975**, the **American College of Chest Physicians** and The **American Thoracic Society Joint Committee on Pulmonary Nomenclature** published the report "*Pulmonary Terms and Symbols*", which included a clear explanation of COPD. Firstly, they defined COPD as *Diagnostic Terms Based on Clinical Findings*, however, upon reviewing the text, it could be more accurately redefined as "*Diagnostic Terms Based on Lung Function*". Specifically, both committees defined COPD as "*refers to diseases of uncertain etiology characterized by persistent slowing of airflow during forced expiration*"; in contrast to asthma, which *"changes in severity either spontaneously or as a result of therapy*" [38]. These definitions laid the base of a **functional definition of COPD**, although not fixing any cut-off, but abandoning the previous anatomical (emphysema) and clinical/etiological ("chronic bronchitis") ones.

The above definitions allowed, among others, one of the most remarkable studies that would significantly influence the approach to the disease in the following years. In **1977, Fletcher and Peto** published a remarkable study evaluating the **FEV_1** and suggesting a **gradual and physiological decline throughout life**. However, the most relevant statement of their work was that **susceptible smokers developed a significantly more pronounced airflow obstruction**, leading to markedly lower values over time [39], consistent with the results of the **Framingham Study** [24]. Importantly, they noted that **smoking cessation did not fully restore lost lung function**, but it did normalise the rate of decline in FEV_1. This finding highlighted that **early detection** and smoking cessation in middle-aged individuals **could prevent severe or fatal COPD**. Additionally, it reinforced the perception of COPD as a **chronic progressive disease** that was **largely irreversible** (or only minimally reversible) and **focused COPD on smoking** in a more significant way than the previous ones [39].

Nonetheless, it must be noted that several authors debated whether **COPD** should be defined as a combination of previous entities (emphysema and chronic bronchitis) **without reference to lung obstruction**, or whether **asthma** should also be incorporated **into an omnibus term with COPD**. These debates have persisted and remain unresolved to this day. **Nevertheless, the most widely accepted framework was ultimately established through the GOLD initiative**.

2.4 The Global Initiative on Chronic Obstructive Lung Disease (GOLD)

COPD was not receiving the attention it required compared with other chronic diseases, despite being a leading cause of morbidity and mortality in the late twentieth century. In **1997, the Global Initiative on Chronic Obstructive Lung Disease (GOLD)** was launched with the aim of raising the profile of COPD among the medical community and government authorities and *"to form an independent global network of individuals and organisations committed to increasing*

awareness of COPD among health professionals, health authorities, and the general public; improving diagnosis, management and prevention; stimulating research; and providing evidence-based educational resources concerning COPD for worldwide use" .[40]

A committed group of experts, led by **Romain Pauwels**, spearheaded the initiative. This team persuaded the **US National Heart, Lung, and Blood Institute (NHLBI)**, directed by **Claude Lenfant**, and the **World Health Organisation (WHO)**, with **Nikolai Khaltaev** as director, to support the development and establishment of GOLD. The organisation was created as a **think tank** under the guidance of **Suzanne S. Hurd**, who oversaw its initial design and implementation[41].

The first objective of **GOLD** was to produce a consensus report entitled *Global Strategy for the Diagnosis, Management, and Prevention of COPD*. This strategy sought to improve diagnosis and management of the disease, to increase awareness among healthcare professionals, health authorities, and the general public, and to stimulate research. It also aimed to provide **evidence-based educational resources** for worldwide application.

From its inception, **GOLD** was established as a **non-profit organisation** and adopted a collaborative approach involving professional health organisations, patient associations, and healthcare agencies. One of GOLD's core principles was to provide a **flexible and adaptable strategy** suitable for diverse global contexts, recognising that it is not feasible to establish uniform clinical guidelines for all countries due to variations in healthcare resources and practices.

GOLD's work was considered **revolutionary** because it produced a **global reference document** for the diagnosis and management of **COPD**. Although it was not conceived as a standard clinical guideline, the **GOLD Report** had a profound impact by establishing a **common clinical framework**, promoting a **standardised approach** for homogeneous criteria in studies, and disseminating **best practices** worldwide.

The **GOLD Report**, first published in **2001**, has undergone major modifications every **four to five years** and is updated **annually**. The most notable revisions in disease assessment methods occurred in **2006, 2011, 2017, and 2023** (Table 1). Nonetheless, its most important contribution to the present discussion was the inclusion of a **standard definition of COPD** and a **final diagnostic criterion**.

Table 1 Evolution of COPD definition and Diagnostic criteria in GOLD guidelines (2001-2023)

Year	Definition (main paragraph + subsequent paragraphs summary) (*)	Diagnostic criteria
2001 [40]	*"COPD is a disease state characterized by **airflow limitation that is not fully reversible**. The airflow limitation is usually both **progressive** and associated with an **abnormal inflammatory response** of the lungs to **noxious particles or gases**."* **Summary**: No mention of *emphysema* or *chronic bronchitis*. Focus on spirometry as confirmatory diagnosis.	- **Suspicion**: Symptoms of cough, sputum production, or dyspnoea, and/or history of exposure to risk factors. - **Confirmation**: Post-BD spirometry: FEV_1 < 80% predicted and FEV_1/FVC < 70% (or clinical approaches if not feasible). - If not confirmed but at risk or symptomatic: category **GOLD 0**.
2006 [42]	*"Chronic obstructive pulmonary disease (COPD) is a **preventable** and **treatable disease** with some **significant extrapulmonary effects** that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases."* **Summary**: *Emphysema* and *obstructive bronchiolitis* considered causal. Increased attention to comorbidities in older patients and smokers.	- **Elimination of GOLD 0** ("at risk") category. - **Additional investigations in selected cases**: CT, chest X-ray, and/or α_1-antitrypsin deficiency screening.
2011 [43]	*"COPD, a **common** preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced **chronic** inflammatory response in the airways and the lung to noxious particles or gases. **Exacerbations and comorbidities contribute to the overall severity in individual patients**."*	- **Confirmation**: Post-BD spirometry: FEV_1/FVC < 70%. - **Spirometry is required** to make the diagnosis. - **FEV_1 threshold excluded** as diagnostic criterion.

	Summary: *Idem* plus Chronic inflammation produces structural changes, loss of elastic recoil, and difficulty maintaining airway patency during expiration.	
2017 [44]	*"COPD is a common, preventable and treatable disease that is characterized by **persistent respiratory symptoms** and airflow limitation that is due to **airway and/or alveolar abnormalities** usually caused by significant exposure to noxious particles or gases."* **Summary**: *Idem* plus Chronic respiratory symptoms may precede airflow limitation. **Exacerbations not included in the definition**.	No major changes.
2023 [45,46]	*"Chronic Obstructive Pulmonary Disease (COPD) is a **heterogeneous lung condition** characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, **often** progressive, airflow obstruction."* **Summary**: **Inexistent**. **No reference** to *significant exposure to noxious particles or gases* as a cause.	No major changes. Clarifies that not fully reversible airflow obstruction is not exclusive to COPD. FEV_1/FVC ratio between **0.6–0.8** should be reconfirmed. Although some authors proposed the **lower limit of normal (LLN)**, GOLD maintains **0.7** as the preferred diagnostic threshold.

(*) Emphases added: **Bold text** highlights novelty changes, while underlined text indicates elements already present in previous versions. *Italy* means exact transcription.

The development of the **GOLD guidelines** from **2001 to 2022** reflects the progressive advancement in the understanding of **COPD**. As previously noted, COPD was initially defined with an emphasis on **non-reversible airflow limitation** and its association with the **inflammatory response** to exposure of the lungs to **noxious elements**.

In the early versions, **spirometry** was emphasised as the key diagnostic tool, with strict thresholds based on **FEV_1** and the **FEV_1/FVC ratio of 0.7** [40,42] Over time, GOLD integrated the importance of **concurrent diseases** and the **systemic impact of COPD**, while moving away from using FEV_1 as a diagnostic criterion (although it remains a classification factor, as explained later). At the same time, GOLD reinforced the requirement, rather than the suggestion, of spirometric confirmation [43].

In **2017**, it was acknowledged that **chronic respiratory symptoms may appear before airflow obstruction**, admitting that certain individuals may exhibit **structural modifications in the lung** without corresponding abnormalities on spirometry, and thus would not be labelled as COPD [44]. Nonetheless, the definition remained relatively stable until **2022**, when a **major change** was introduced.

2.5 2022 next generation definition: the decline of noxious particles or gases in the definition of COPD

In **2022, Celli et al.** proposed a substantial revision to the definition of **COPD**. The authors argued that the traditional definition (focused primarily on **irreversible airflow limitation** attributed to **smoking**) fails to reflect the full **complexity and heterogeneity** of the disease. They emphasised that other factors, including **biomass exposure, poverty, respiratory infections** (e.g., **tuberculosis**), **asthma**, and even **altered early lung development during childhood and adolescence**, also contribute to the onset of COPD, particularly among **women** and in regions where smoking is not the predominant risk factor [13].

They further suggested that this broader perspective may explain why, despite decades of research, the **morbidity and mortality associated with COPD** have not declined at the same rate as those of other chronic conditions, such as **cardiovascular disease** or certain forms of **cancer** [13].

It therefore presents **COPD** as a **"syndrome" rather than a "single disease"**, given its heterogeneous nature and diverse underlying causes. While maintaining the current nomenclature, an **aetiological classification** has been introduced to address the need for **specific therapies** tailored to each type of COPD, instead of applying a universal approach based mainly on smoking history[13]:

- **Genetic COPD (COPD-G):** Associated with genetic alterations such as **α_1-antitrypsin deficiency (SERPINA1)**, which predisposes to the development of **emphysema** and COPD, particularly in **young individuals** and smokers.
- **COPD due to abnormal lung development (COPD-D):** Originates from **abnormal lung development** influenced by **environmental exposures, recurrent infections, malnutrition**, or **genetic factors** during childhood and adolescence.
- **Cigarette smoking COPD (COPD-C):** The best-studied form of COPD, usually caused by an **abnormal inflammatory response** to **tobacco smoke**. Mechanisms include **protease–antiprotease imbalance, autoimmunity**, and **accelerated lung ageing**.

- **Biomass and pollution exposure COPD (COPD-P):** Associated with exposure to **biomass fuels and air pollution**. Particularly prevalent in certain world regions and among **women**. Characterised by **less emphysema** and greater **airway involvement**.
- **COPD due to infections (COPD-I):** Linked to **previous infections**, such as **respiratory syncytial virus** in childhood or **tuberculosis**. May involve **abnormal repair processes**, leading to **fibrosis** and **distortion of lung parenchyma**.
- **COPD with asthma (COPD-A):** Includes patients with **uncontrolled asthma** who develop **chronic airflow limitation**, and those with overlapping features of both asthma and COPD, such as **reduced elastic recoil** and **emphysema** (commonly referred to as **asthma–COPD overlap, ACO**).
- **COPD of unknown cause (COPD-U):** Refers to cases where **no known risk factors** are identified; considered **idiopathic** until further evidence emerges.
- **COPD of mixed causes (COPD-M):** Involves patients with **multiple causal factors**, requiring a **comprehensive assessment** to identify predominant **pathobiological mechanisms** and design **personalised therapies**.

The other major criticism concerns the need to **identify COPD early**, before airflow limitation becomes evident on **spirometry**. The concept of **"pre-COPD"** was introduced, reviving an idea already present in **GOLD 2001** (later abandoned), to refer to individuals with **respiratory symptoms** or **structural abnormalities** detectable by **computed tomography (CT)** but without clear spirometric obstruction [13]. The principal aim of this concept is to enable **earlier and more preventive interventions**, addressing a gap that previous definitions had not sufficiently covered.

All these proposals were subsequently incorporated into the **next version of GOLD (2023)**, which thus became the **current definition** [45,46].

3 Current challenges around the spirometry required a search of alternative gold standards

Despite being considered the **"gold standard"**, the **FEV_1/FVC ratio** has significant limitations that may lead to both **overdiagnosis and underdiagnosis** of the disease. Emerging evidence suggests that incorporating **additional pulmonary function tests** and **biomarkers** could improve diagnostic accuracy [47,48]. The use of **spirometry** for COPD diagnosis presents several **limitations and challenges**, including issues related to **sensitivity**, **specificity**, and the **practical difficulties** in test execution. Furthermore, the reliance on fixed thresholds for diagnosis can result in **misclassification**, particularly in heterogeneous

populations. These shortcomings underscore the need for **complementary diagnostic methods** and a more **nuanced interpretation** of spirometry results.

3.1 Patient-related challenges

Spirometry requires **maximal effort** during the **forced expiratory manoeuvre**, which can be particularly challenging for **older adults** or patients with **physical or cognitive limitations**. Test results may also be influenced by **muscle fatigue** and **impaired coordination**, factors that affect spirometry performance in approximately **40% of individuals over 65 years of age** [49]. This is particularly relevant given that **59% of patients with COPD worldwide**, **42% in the USA**, and **73% in Spain** are aged over 65 years[1][50,51].

In addition, the use of certain medications—such as **β-blockers**, with or without **β-agonists**—prior to pulmonary function testing may adversely affect results and potentially lead to **misdiagnosis**. Patients are rarely instructed to refrain from such medications before testing, and consequently often administer them shortly before the examination [52].

It is also important to acknowledge the influence of **ethnic variability**. Distinct lung capacities across different ethnic groups are not adequately accounted for in current predictive equations, which compromises the accuracy of pulmonary function tests and increases the risk of **diagnostic error** [53].

3.2 Diagnostic cut-off FEV_1/FVC vs LLN and other spirometry-related controversies.

Relatively recently, there has been **controversy** regarding the use of a **fixed cut-off for the FEV_1/FVC ratio** to define airflow obstruction in **COPD**, as the **lower limit of normal (LLN)** for this ratio decreases with advancing age[45,54,55]. **FEV_1** typically declines with age, and its rate of decline serves as an important spirometric marker of disease progression in COPD. In healthy non-smokers, the decline is approximately **30 mL per year**, with an upper threshold of around **50 mL per year**; reductions exceeding this are considered **accelerated** [39,54].

According to some authors, this situation leads to **underdiagnosis in younger individuals** and **overdiagnosis in older individuals** when a fixed threshold is used. Several authors have argued that patients classified as having COPD by the fixed threshold of **FEV_1/FVC <0.70**, but not according to the LLN, do not present clinically significant COPD, suggesting that reliance on the fixed threshold contributes to overdiagnosis[49]. Others contend that patients included by the LLN but not by the fixed threshold exhibited **significant clinical problems**, including

[1] These percentages were calculated using age-stratified COPD prevalence data (65–74 years, ≥75 years, and all ages) from the Global Burden of Disease 2021 (for Spain and global estimates) [50], and from a U.S. national study [51].

persistent respiratory symptoms, and therefore should not have been considered false positives [55].

In **2014, the Global Lung Initiative (GLI)** proposed the use of **z-scores** to define normal spirometry values (i.e. FEV_1, FVC, and FEV_1/FVC). Z-scores indicate the number of standard deviations a measured value deviates from the mean of the reference population. Their findings suggested that use of a fixed ratio (0.7 for FEV_1/FVC) may result in **misclassification** of individuals as having respiratory impairment [46,56].

Consequently, the **ERS** and **ATS** incorporated into their spirometry and lung function testing standards the use of **LLN = 5th percentile** and **ULN = 95th percentile** as the normal range, explicitly discouraging reliance on the fixed threshold of FEV_1/FVC <0.7. They also recommended the use of **z-scores** to grade the severity of lung function impairment (i.e., FEV_1 and DLCO: *Mild* −1.65 to −2.5; *Moderate* −2.51 to −4.0; *Severe* <−4.1) [57,58].

However, **GOLD rejected these recommendations**, maintaining that the fixed threshold of **FEV_1/FVC <0.7** is **simpler, easier to interpret, and independent of reference values**, as it only requires comparison of variables measured in the same patient. GOLD also emphasised that all major clinical studies forming the evidence base for treatment recommendations have relied on this fixed ratio. Conversely, they argued against the use of LLN and z-scores because their validity depends heavily on the reference equations used, and the clinical relevance of classification differences remains unclear. Thus, GOLD has continued to advocate for the fixed ratio, citing **simplicity and consistency for "busy clinicians"**[59].

A review of this controversy highlighted two main issues: first, that much of the research aiming to validate LLN as superior did not employ **post-bronchodilator spirometry**, thereby failing to comply with GOLD standards; and second, that individuals with **FEV_1/FVC <0.7 but above the LLN** had an **increased risk of death and hospitalisation** due to exacerbations. Nevertheless, more recent studies suggest that using the fixed cut-off (<0.7) is neither significantly superior nor inferior to LLN-based thresholds in predicting **COPD-related hospitalisations or mortality** [55,60,61].

Some researchers further argue that conventional spirometry underutilises the information available from the **expiratory flow–volume curve**, and propose alternative indices, including **FEV_1/FEV_6**, **FEV_1/FVC_3**, the **D parameter**, **flow decay**, **AUC_3/AT_3**, the **area under the expiratory flow–volume curve (AEX)**, and the **maximal expiratory flow–volume curve (MEFV)**, among others [47,55].

Perhaps the most candid statement regarding this controversy is that "from a scientific or clinical perspective, it is difficult to determine which of these criteria will result in optimal COPD diagnostic accuracy" [59].

Further divergence exists regarding the **criteria for selecting the best FEV_1 or FVC values** in spirometry. Both **GOLD** and **ERS/ATS** recommend repeat tolerance criteria to validate results [57–59]. However, the ERS/ATS guidelines stipulate a repeatability tolerance of **0.150 L for FEV_1 and FVC** [58], while GOLD requires **0.150 L or 5%, whichever is greater** [59], increasing above 3 L the variability [57]. Moreover, ERS/ATS standards specify that FEV_1/FVC should be derived from the **highest recorded FEV_1 and FVC**, even if obtained from different manoeuvres [58], whereas GOLD stipulates that FEV_1/FVC must be calculated from the manoeuvre yielding the **highest sum of FVC and FEV_1**[59].

Another challenge is the **selection of reference equations** for predicted spirometric values. **Roca et al. (1998)** demonstrated that applying different equations could drastically alter results [62]. Several formulations have been published, including those of **Baldwin (1948), Goldman (1959), Grimby (1963), Crapo (1982), and Quanjer (1993)** [29,63–66]. Roca also developed the widely used equation for **Mediterranean populations (1998)** [62]. Currently, most studies use the **GLI multi-ethnic reference equations (2012)** [67] which were derived for **Caucasians, African Americans, Northeast Asians, Southeast Asians**, and an **"Other/mixed"** group, albeit with evident limitations. More recently, the **GLI (2022–2023)** released a new global, **race-neutral equation**, although it still requires validation and the 2012 version remains the most widely applied [68].

In addition, regardless of the cut-off used or the spirometric protocol followed, it should be noted that a population-based study in Spain found that up to 16% of individuals initially diagnosed with COPD by spirometry reverted to normal values within four weeks, suggesting misclassification as false positives [69].

Overall, despite diverse findings, these divergences illustrate how reliance on a **single spirometry-derived diagnostic criterion** may contribute to both **misdiagnosis and underdiagnosis**, particularly in **primary care**.

3.3 Real-life underutilisation of spirometry and its causes

Nevertheless, the most significant problem related to the spirometric criterion is the **underutilisation of spirometry**, which frequently results in patients being **diagnosed or treated as COPD without confirmatory testing**. Table 2 presents a simple, non-systematic review of spirometry utilisation rates in COPD diagnoses, including both **population-based** and **retrospective studies** of patients labelled or treated as COPD.

Table 2 Simple non-systematic review of spirometry utilisation in COPD diagnoses.

Country	USA		Canada (Ontario)	Spain	Swedish		Israel	China	South Korea
Diagnosis with spirometry (%)	32.0	59.7 (*)	41.2	45.6	59.0	88.0	44.6	18.3	57.0
Years (Data)	2002-2003 [70]	2012-2015 [71]	2005-2012 [72]	2010 [73]	2000-2003 [74]	2004-2010 [75]	2015-2018 [76]	2013 [77]	2008 [78]

(*) This Canadian sample population was restricted to veterans, theoretically with easier access to spirometry.

Several studies indicate that **general practitioners (GPs)** often diagnose COPD or asthma primarily on the basis of the **patient's clinical presentation**—typically over a prolonged period and/or following a therapeutic trial—while perceiving spirometry results as having **limited clinical value** [79,80]. This perception persists despite evidence from other studies showing that GPs are aware of spirometry's importance in respiratory diseases [80].

Another major limitation is **insufficient proficiency** in both the performance and interpretation of spirometry, particularly in **primary care** [48,49]. Nevertheless, when adequately trained, nurses, technicians, and GPs in primary care settings can competently detect **chronic airflow obstruction** [48]. Even so, GP confidence in spirometry —particularly in **interpretation rather than execution**— remains low, sometimes persisting despite repeated training provided by respiratory specialists [80,81].

Logistical challenges also contribute to underutilisation. The time required to inform patients about the need for spirometry, explain the technique, administer the test, allow for bronchodilator effects, repeat testing, and interpret the findings is a recognised barrier. This problem is compounded by the **limited availability of trained staff**, the frequent absence of **on-site spirometers** or readily accessible referral centres, and the **long waiting times** that ensue. As a result, **patient attendance rates** decline [71,80,81].

Finally, **cost** poses another obstacle. The expenses of consumables, professional time, and equipment acquisition have been highlighted as relevant barriers, especially in settings where patients rely on **private healthcare** or where spirometry is not covered by **public health services or insurance** [71,80,81].

3.4 Searching alternatives to spirometry: imaging focus

In **2019, COPDGene** introduced an alternative categorisation of COPD based on available evidence, requiring a **probable exposure history, CT imaging,**

symptomatology, and spirometry results. They proposed classifying the degree of evidence as **possible, probable, or definite COPD**. According to their findings, the most relevant factor for predicting **chronic progression**—and therefore most closely linked to COPD—is the **presence of symptoms**, followed by **computed tomography (CT) findings**, whereas **spirometry remains the primary predictor of mortality**. However, they adhered to the **2006 GOLD criteria**, which included **FEV_1 <80% predicted** as a diagnostic threshold (subsequently excluded in later definitions) [82].

Some authors have suggested that **CT should become the diagnostic standard for COPD** [55]. **Quantitative computed tomography (QCT)** provides detailed assessment of **emphysema, vascular involvement, and airway disease**, although its application is still evolving. Additional features of interest measurable by imaging include **atherosclerosis, cachexia, and osteoporosis**. Techniques such as the **density mask (−950 HU)** and the **15th percentile index** allow quantification of emphysema and have been shown to be reliable **predictors of mortality**.

Multiple studies demonstrate that **centrally located emphysema** correlates more strongly with airflow limitation than **peripheral emphysema**. In the assessment of **airway disease**, parameters such as **bronchial wall thickness** and the **extent and distribution of air trapping** are being investigated. One of the earliest and simplest methods to estimate air trapping using chest CT involves measuring the **percentage of low-attenuation areas** with a threshold of **−856 HU or −850 HU**. These values represent the attenuation of a normally inflated inspiratory lung; a healthy expiratory lung is expected to show attenuation values above this threshold, which correlate well with spirometry.

While CT has proven useful for assessing **small airway disease**, it faces technical challenges in differentiating between **air trapping** and **emphysema** [83]. Other functional imaging modalities, particularly **positron emission tomography (PET)** and **magnetic resonance imaging (MRI)** —including **hyperpolarised gas MRI**—offer potential insights into **regional lung perfusion, ventilation, and inflammation**, with MRI providing the advantage of **no radiation exposure** [84,85].

Nevertheless, *in vivo* imaging of microscopic structures does not directly guide **therapeutic strategies**, since imaging alone does not elucidate the **underlying mechanisms** or clarify the significance of these findings in disease onset or progression. Consequently, imaging has had **limited impact on personalised therapy**. Currently, apart from **lung volume reduction surgery**, no treatments rely on imaging-derived insights. Compared with simply testing the drug in question, the **risk–benefit ratio** of thoracic imaging remains unfavourable [86].

Moreover, **CT is not universally and permanently available** [55], and long **waiting lists** further restrict access. Its role appears limited to **specific subgroups**, such as

patients with COPD and **α_1-antitrypsin deficiency** [59,86]. Still, structural information obtained from imaging should not be entirely dismissed, as it may prove crucial for **accurate characterisation and phenotyping** of COPD. This could facilitate the identification of **biomarkers** for disease activity or **genetic associations**, supporting **pathway discovery** and paving the way towards research in **direct biological markers**.

4 COPD Diagnosis status and challenges: Prevalence, Underdiagnosis, Late-diagnosis and Misdiagnosis

The **heterogeneity of COPD**, its **definitional variability**, and the **limitations of spirometry**—together with related controversies—contribute to substantial levels of **underdiagnosis and misdiagnosis**. These issues also complicate the accurate estimation of **COPD prevalence**.

4.1 Prevalence

COPD is a globally prevalent condition, and its burden continues to grow, underlining the importance of precise epidemiological assessment. The **Global Burden of Disease (GBD) Study**, one of the most comprehensive international analyses, reported in its 2021 update that COPD ranked **32nd among 169 documented conditions** by prevalence, rising from **42nd in 1990** across all age groups. Among individuals aged over 40 years, it advanced from **27th to 23rd position** in the same period.[50,87]

The GBD 2021 study estimated a total of **213,387,446 people living with COPD** (95% CI: 194,868,122–233,975,905), of whom **196,583,422 (95% CI: 173,960,193–219,290,642)** were over 40 years of age. This corresponds to an estimated prevalence of **2.80% (95% CI: 2.56–3.07)** for the general population and **6.78% (95% CI: 6.00–7.56)** for those aged >40 years [87].

However, these estimations are lower than those reported in specific **meta-analyses** that focused on population-based, spirometry-confirmed prevalence. A recent meta-analysis estimated prevalence at **12.64% (95% CI: 10.75–14.65)** among adults over 40 years [6], aligning with earlier findings such as **10.3% (95% CI: 8.2–12.8)** for individuals >30 years, corresponding to **391.9 million (312.6–487.9 million) cases** in 2019 as reported by **Adeloye et al. (2022)** [2]. Similarly, **Boers et al. (2023)** estimated prevalence at **10.6% (479.9 million people)** in 2020 [88].

To illustrate how prevalence varies across **sex, age, smoking status, and WHO regions**, Table 3 presents pooled estimates from a meta-analysis [6], comparing **fixed-ratio (FR <0.7)** and **lower limit of normal (LLN)** diagnostic criteria.

Table 3 Prevalence of COPD in adults ≥40 years by sex, age group, smoking status, and WHO region, according to FR and LLN criteria.

	FR criteria			LLN criteria		
	Total number of participants	Prevalence of COPD % (95% CI)	I_2 (%)	Total number of participants	Prevalence of COPD % (95% CI)	I_2 (%)
Sex group						
All	200,723	12.64 (10.75–14.65)	99.34	164,184	7.38 (5.47–9.553)	99.42
Male	77,353	15.47 (12.22–19.02)	99.29	57,583	8.67 (8.44–8.90)	94.75
Female	74,597	8.79 (6.94- 10.828)	98.58	57,583	8.00 (6.42–9.73)	96
Age group						
40–49 years	18,287	4.37 (2.76–6.33)	96.46	2715	5.22 (2.34–9.17)	93.02
50–59 years	16 362	9.54 (6.70–12.82)	97.21	2173	6.61 (2.05–13.51)	96.39
60–69 years	11,920	15.84 (11.85–20.29)	97.04	1478	14.29 (12.54–16.17)	78.95
70 years and older	5923	24.03 (20.04–28.26)	91.6	852	14.23 (11.96–16.75)	79.49
Smoking status						
Never smokers	55,903	8.15 (5.57–11.18)	98.59	69,308	3.78 (0.37–10.53)	99.81
Former smokers	11,484	18,38 (12.03–25.73)	98.42	42,159	7.55 (3.00–13.96)	99.46
Currently smokers	26,370	21.51 (16.39–27.12)	97.93	7575	11.13 (5.02–19.27)	98.14
WHO region						
Eastern Mediterranean Region	No reported	7.95 (3.72–13.59)	95.24	No reported	6.90 (0.04–0.11)	83.34
European Region		13.09 (8.32–18.76)	97.63		7.34 (6.7–8.01)	95.86
Americas Region		22.93 (8.18–42.34)	99,77		4.82 (0.49–13.23)	99.8
Southeast Asia Region		19.48 (7.99–34.47)	98.65		10.17 (2.22–22.94)	98.63
Western Pacific Region		11.17 (9.11–13.42)	99.42		7.56 (3.70-10.11)	94.96
African Region		-	-		7.70 (6.0–9.8)	-

Adapted from [6]. Abbreviations: COPD: chronic obstructive pulmonary disease; FR: fixed ratio; LLN: lower limit of normal; WHO: World Health Organisation.

In **Spain**, prevalence is estimated at **11.8%** overall, with **9.4% in women** and **14.6% in men** using FR; by LLN criteria, prevalence is **6.0%, 4.9%, and 7.1%**, respectively [89].

COPD risk varies substantially across demographic groups, largely influenced by **regional tobacco use patterns**. Despite preventive measures, smoking prevalence continues to rise, particularly in **low- and middle-income regions**. Other important risk factors include **air pollution, occupational exposure, asthma, allergies, severe paediatric respiratory infections, and tuberculosis** [88]. Nonetheless, **smoking accounts for 60–70% of the global burden of COPD**, according to GBD [90].

The ongoing **debate on diagnostic thresholds** for spirometry contributes to **discrepancies in prevalence estimates**. Still, consistent patterns emerge across studies: COPD is more common in **men** (by FR), in **older adults**, and in **current or former smokers** (both criteria), with FR yielding consistently **higher prevalence estimates** than LLN [2,6,88–90].

Looking ahead, global **COPD prevalence is projected to rise further**, with **women** and populations in **low- and middle-income countries** facing disproportionately higher growth rates [88].

4.2 Underdiagnosis

Nonetheless, the main challenge in COPD remains its **high level of underdiagnosis**, which is probably the principal reason why the **GBD Study** reports comparatively lower prevalence figures. For this report, a **non-systematic review** was conducted to evaluate the current status of underdiagnosis, and the results are summarised in Figure 2 and Table 4.

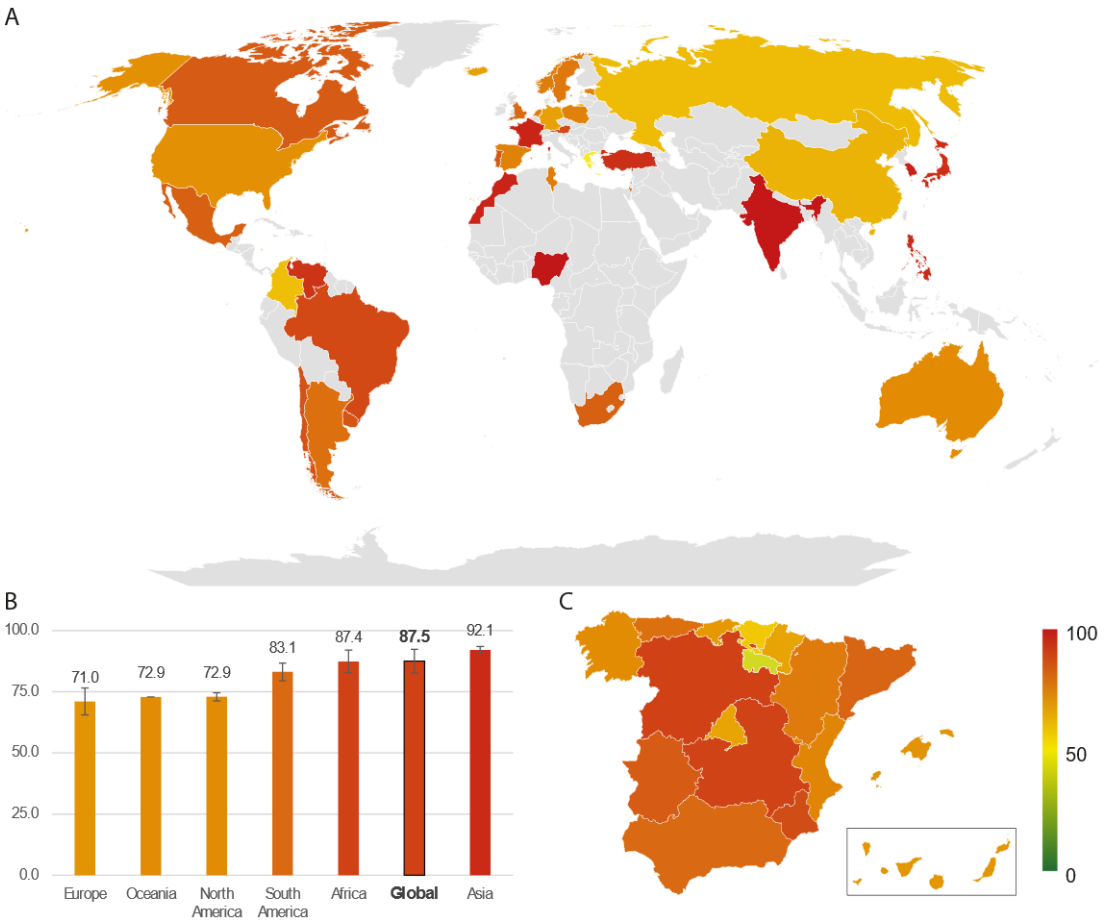

Figure 2 Underdiagnosis of COPD worldwide, by continent, and in Spain.
(A) Underdiagnosis rates by country. (B) Weighted mean and weighted standard deviation of underdiagnosis rates by continent. (C) Underdiagnosis in Spain. Global data were obtained from **multiple sources** [91–102], while Spanish statistics were drawn from the **EPISCAN II study** [89]. When multiple publications existed for a country, only the most recent was included. When data from several cities within a single country were available in the same study, a weighted average was computed. Weighted values in panel B were calculated from the total number of individuals with valid spirometry. The same colour scale is applied throughout the figure, with grey representing countries or regions with no available data. Detailed data are shown in Table 4.

Table 4 Underdiagnosis of COPD (%) by country and continent.

Continent / Country	COPD Underdiagnosis (%)	Total Subjects with Spirometry measured	Source
Africa	**87.4 ± 9.2**	**2,869**	
Morocco	93.7 §	477	102
Nigeria	98.3	885	91
South Africa	81.4	847	91
Tunisia	75.8	660	91
Asia	**92.1 ± 2.8**	**132,880**	
China	64.9	473	91
India	97.0 *	2,033	91
Israel	78.4 §	1,058	92
Japan	91.6	102,190	101
Philippines	92.3 *	1,615	91
Russia	63.3 #	251 #	96,97
South Korea	95.2	24,454	100
Turkey	91.3	806	91
Europe	**71.0 ± 11.0**	**22,104**	
Austria	85.9	1,258	91
Estonia	74.4	615	91
France	94.0	763	99
Germany	68.9	683	91
Greece	53.2 §	5,226	98
Iceland	68.7	757	91
Netherlands	75.7	590	91
Norway	75.6	658	91
Poland	75.0	526	91
Portugal	82.9	712	91
Spain	74.7 §	9,092	89
Sweden	76.5	547	91
United Kingdom	79.6	677	91
North America	**72.9 ± 3.3**	**15,212**	
Canada	82.4	827	91
Mexico	81.6	1,000	91
United States	71.7 §	13,385	95
Oceania	**72.9 ± 0.0**	**541**	
Australia	72.9	541	91
South America	**83.1 ± 7.2**	**3,817**	
Argentina	78.0 §	446	93,94
Brazil	86.0	963	91
Chile	84.2	1,173	91

Colombia	62.8 §	326	93,94
Uruguay	83.3 §	103	93,94
Venezuela	90.4 §	665	93,94
Global	**87.5 ± 9.7**	**177,423**	

Continents and countries are listed alphabetically. Results are summarised as weighted mean ± weighted standard deviation, based on the total number of subjects with valid spirometry per country. Legend: * = calculated weighted mean; # = unclear data; § = diagnosis based on GOLD fixed criterion FEV_1/FVC <0.7.

Globally, a high level of underdiagnosis was identified (**87.5% ± 9.7%**), with significant differences across continents (p<0.001, Kruskal–Wallis; range: 71.0–92.1%) and across countries (p<0.001, Kruskal–Wallis; range: 53.2–98.3%). In Spain, underdiagnosis was somewhat lower (**74.7% ± 11.2%**) but comparable to that of most European countries (**71.0% ± 11.0%**). The Spanish situation appears stable, with no significant changes compared with the earlier **EPISCAN I** survey [89].

As this analysis is not systematic, other publications may exist that were not included. Another limitation is that no distinction was made between studies using **LLN** or **fixed-ratio** criteria, although the fixed ratio was preferred when both were available.

A **post hoc analysis** performed for this report, using **weighted least-squares regression** from studies that reported both LLN and fixed ratio [89,94], showed higher underdiagnosis levels with the fixed ratio, although this difference did not reach statistical significance (**+5.3%, 95% CI −1.67–12.16%, p=0.132**). Weights were assigned according to the number of COPD cases diagnosed by each criterion (fixed ratio or LLN), as underdiagnosis was defined in relation to the diagnosed population, and this information was consistently available. As no statistically significant differences were observed, the findings of this review should not be affected by combining both criteria. The **fixed ratio** was therefore preferred, as LLN depends heavily on the chosen reference equation, which limits comparability. Moreover, the fixed ratio remains the most widely used criterion worldwide and in most research studies.

As noted in earlier sections, **the main driver of underdiagnosis is the underuse of spirometry**. Additional factors associated with underdiagnosis include **age extremes** (younger and older adults), **male sex**, **ethnic minority status** (e.g. Afro-Latin Americans) [94,95], **lower educational level**, **living alone** [89,103], **minimisation of symptoms** or self-reporting as "asymptomatic", often associated with better FEV_1 values, and **lighter smoking history**. At the global level, COPD remains disproportionately underdiagnosed in **developing regions** [88].

Conversely, greater risk of underdiagnosis has also been linked to being a **current smoker** and having more **comorbidities** such as depression or asthma.

Supporting this, a recent meta-analysis found that the pooled prevalence of COPD underdiagnosis among smokers with spirometric evidence of COPD—but without a medical diagnosis—was **16% (95% CI: 14–18%)**, and even higher (**25%, 95% CI: 22–28%**) among patients receiving **inhaled treatments for asthma** [104].

4.3 Late diagnosis

A derivative consequence of COPD underdiagnosis is its frequent **late diagnosis**. Several studies agree that a substantial proportion of COPD patients remain undiagnosed for years, even after multiple clinical opportunities to identify the disease. **Jones et al. (2014)** reported that **85% of UK patients** diagnosed with COPD between 1990 and 2009 had previous consultations for respiratory symptoms, antibiotic or steroid prescriptions, or imaging studies more than **10 years before the diagnosis was established** [105]. This finding is illustrated in Figure 3. A subsequent study in the UK (2011–2014) confirmed this trend, observing that **67% of patients** were diagnosed late, having presented several clinical indicators at least five years before diagnosis [9].

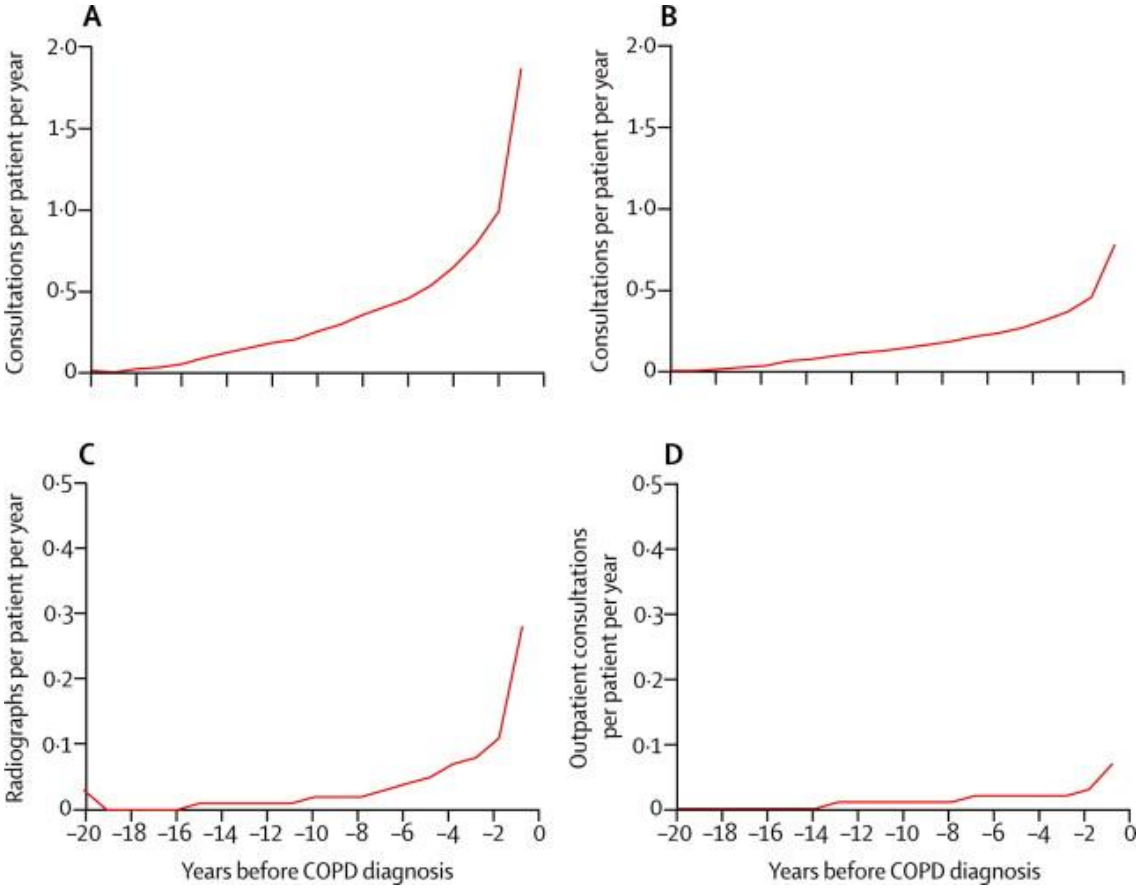

Figure 3 Mean frequency of missed opportunities to diagnose COPD.
(A) Consultations for lower respiratory symptoms; (B) lower respiratory prescribing consultations; (C) chest radiography; and (D) outpatient consultations. Extracted from [105].

This issue is not limited to the UK. Although relatively few studies are available, **Chinese** and **Swedish** cohorts reported similar results. In China, the **median diagnostic delay was 230 days (IQR: 50–720)**, indicating that even in tertiary hospitals, recognition of COPD may be substantially delayed [106]. In Sweden, more than **two-thirds of patients** were classified as late diagnosed, presenting with ≥3 clinical indicators before diagnosis [107].

The main explanations for late diagnosis of COPD can be grouped into three domains: **patient-related**, **healthcare system–related**, and **disease-related** factors.

- **Patient-related factors:** *Roucoux et al. (2025)* identified barriers such as **lack of knowledge** about COPD, **denial of symptoms**, and **fear of receiving a lung cancer diagnosis** [81]. Similarly, *Dai et al. (2021)* found that **low educational level** and **living alone** were significantly associated with diagnostic delays, highlighting the role of health education and social support in seeking medical care [106].
- **Healthcare system factors:** The most frequently reported issue is the **low use of spirometry**, especially in **primary care**, which remains one of the major obstacles to early diagnosis. *Jones et al. (2014)* showed that only **33% of patients** who had a chest X-ray in the two years preceding diagnosis also underwent spirometry [105]. Similar underuse has been reported in China, where fewer than **50% of patients** received pulmonary function testing at their initial visit, and only **1.5% in first-level hospitals** [106]. In France, additional barriers include the **prioritisation of other conditions perceived as more serious**, **limited diagnostic resources in primary care**, and **delays in referral to pulmonologists** [81].
- **Disease-related factors:** COPD has an **insidious onset** with **non-specific symptoms**, which complicates early recognition. Many patients gradually **adapt to dyspnoea** or chronic cough, underestimating the severity of their condition. *Larsson et al. (2019)* reported that symptoms may persist for years before medical attention is sought [107]. Furthermore, overlap with other conditions such as **asthma** or **heart failure** may obscure initial clinical suspicion [81].

4.4 Overdiagnosis and misdiagnosis

In contrast to underdiagnosis, **overdiagnosis** (also referred to as **misdiagnosis** [108]) of COPD remains a significant challenge, although its prevalence has been less extensively studied. Overdiagnosis refers to situations in which a patient is **labelled as having COPD**, but subsequent **spirometry does not fulfil the requirements of clinical guidelines**.

In **Spain**, the **EPISCAN II study** reported an overdiagnosis rate of **2.6%** [89], whereas a smaller study of 206 primary care patients estimated a much higher rate of **42.7%** [109]. At the global level, a **2023 meta-analysis** of 39 studies including 23,765 patients found that COPD overdiagnosis, according to GOLD criteria, was **42.0% (95% CI: 37.3–46.8)** [110]. Considerable variability was observed across studies (<25%: n=5; 25–50%: n=21; >50%: n=13). A more detailed analysis showed that **overdiagnosis was significantly higher in primary care studies (45.6%; 95% CI: 39.6–51.6)** compared with hospital-based studies (**26.1%; 95% CI: 21.8–30.5**). Such findings inevitably imply a risk of **overtreatment** in these patients [110].

The main driver of COPD overdiagnosis is the same as for underdiagnosis: the **underuse of spirometry** [110]. Other hypothesised factors include **technical errors** in performing or interpreting spirometry, reliance on **clinical diagnosis by older clinicians**, diagnosis in **younger patients** or those with a **non-smoking history**, and the presence of **comorbidities** that may confound interpretation or overlap symptomatically (e.g. **congestive heart failure** or **asthma**) [7].

Some authors have suggested **redefining and broadening the concept of "overdiagnosis"** to incorporate **clinical criteria**, arguing that COPD diagnosis involves more than spirometry alone and that such a redefinition could alter previously reported prevalence estimates [108]. However, as highlighted in this report, **diagnostic criteria rely exclusively on spirometry**, and GOLD explicitly states that the **definition of COPD should not be conflated with its diagnostic criteria** [13,59].

Nevertheless, this debate illustrates how different understandings of the **definition of COPD** can influence diagnosis and alter prevalence estimates. In this context, the cited meta-analysis reported that applying **LLN criteria** yielded even higher overdiagnosis rates of **48.2% (95% CI: 40.6–55.9)** [110]. Should future changes in diagnostic criteria be adopted, much of the existing research would need to be **re-examined and reinterpreted**.

4.5 Real global clinical diagnosis performance and clinical impacts

A global summary of the current diagnostic situation in COPD can be obtained by constructing a **confusion matrix** for both the worldwide and Spanish contexts. This approach enables the evaluation of the **current real-world diagnostic performance**, using the same analytical framework applied to other diagnostic tests. (Table 5, Appendix 3)

Table 5 Medical current real-life performance diagnosing COPD according to the reported data.

	Sensitivity	Specificity	Precision/PPV	NPV	Accuracy	MCC
Global	12.5%	98.9%	58.0%	90.5%	89.8%	0.24
Spain	25.3%	99.9%	97.4%	90.9%	91.1%	0.47

MCC, Matthews correlation coefficient (also known as the phi coefficient, φ or rφ); PPV, positive predicted value; NPV, negative predicted value.

For global estimations, calculations incorporated the **prevalence of COPD** (10.6) [88], the **global underdiagnosis levels** estimated in this report (87.5%), the recently reported **global overdiagnosis ratio** (42.0%)[110]. For Spain, the corresponding values used were prevalence 11.8%, underdiagnosis 74.7%, overdiagnosis 2.6%, based on **EPISCAN II** [89].

These metrics, combined with the estimated adult population aged ≥40 years worldwide (3.02 Billion)[111] and the Spanish population number (28.3 Millions [111]) allow a **rough estimation** of the distribution of COPD cases according to diagnosis status. (Table 6)

Table 6 Estimated population distribution according to their COPD diagnosis and COPD real condition

	World-wide			Spain		
	COPD	**Without COPD**	**Total**	**COPD**	**Without COPD**	**Total**
Dx	40.00M (1.33%)	28.97M (0.96%)	68.97M (2.28%)	0.85M (2.99%)	0.02M (0.08%)	0.87M (3.07%)
No Dx	280.02M (9.28%)	2.67B (88.44%)	2.95B (97.72%)	2.50M (8.81%)	24.95M (88.12%)	27.45M (96.93%)
Total	320.02M (10.60%)	2.70B (89.40%)	3.02B (100.00%)	3.34M (11.80%)	24.97M (88.20%)	28.31M (100.00%)

B, Billions (100M); M, Millions; Dx, COPD diagnosed

These results are subject to limitations arising from the use of **meta-analyses and aggregate estimates**, and do not account for variability among subpopulations. In the absence of detailed overdiagnosis data by country, this is an acceptable approximation. Importantly, the total estimated COPD population reported here does not differ substantially from the projections of **Boers et al. (2023)** [88] , who employed a more sophisticated approach using subpopulation-specific prevalences. This consistency supports the validity of the estimates and offers a **critical and realistic perspective** of the diagnostic situation, underlining the urgent need for **improved diagnostic accuracy both globally and in Spain**.

The **clinical implications** for patients are evident. **Underdiagnosis, late diagnosis, and overdiagnosis/misdiagnosis** can all lead to significant

consequences, including **anxiety**, **inappropriate treatment**, or a **lack of timely care** [71] Underdiagnosis and delayed diagnosis, in particular, restrict access to early interventions and worsen outcomes [55]. For example, in **Larsson et al. (2019)**, the annual exacerbation rate was **2.67 for late-diagnosed patients** compared with **1.41 for early-diagnosed patients** (HR: 1.89; p<0.001) [107]. Similarly, **Kostikas et al. (2020)** showed that late-diagnosed patients experienced higher risks of **hospitalisation** and greater **healthcare resource utilisation** during the three years following diagnosis.[9]

Conversely, **overdiagnosis/misdiagnosis** often results in **unwarranted use of inhaled bronchodilators and corticosteroids**, exposing patients to **adverse effects** and generating **avoidable healthcare expenditures** [49].

5 COPD classification, management and treatment

Once a diagnosis of COPD is established, patients must be stratified to enable **appropriate management**. In line with the evolution of the **definition and diagnosis of COPD**, classification and treatment recommendations have also changed over time.

Before the **GOLD initiative**, COPD classification followed the older division into two major clinical phenotypes, popularised as **"pink puffers"** (emphysema) versus **"blue bloaters"** (chronic bronchitis). [19] This dichotomy was derived from clinical observations: some C&B (old COPD) patients exhibited **hypoventilation**, with elevated $PaCO_2$ levels and recurrent exacerbations characterised by CO_2 retention, **cyanosis ("blue")**, and **oedema ("bloaters")**, despite minimal emphysema. Conversely, others maintained **alveolar ventilation**, resulting in near-normal $PaCO_2$ and absence of cyanosis (**"pink"**), but significant challenges in sustaining lung ventilation ("puffers") and marked structural emphysema with moderate to mild bronchitis symptoms [112,113]

With the introduction of the COPD concept and the subsequent **GOLD guidelines**, this classification was abandoned in favour of **spirometry-based definitions**, which initially graded disease severity by FEV_1 thresholds and then incorporated additional clinical variables.

The evolution of GOLD classifications and treatment recommendations is summarised in Table 7.

Table 7 Evolution of COPD Classification and management recommendations according to GOLD guidelines

Year	Classification	Treatment (First choice)
2001 [40]	GOLD 0 ("at risk") applies to people lacking diagnostic criteria while exhibiting symptoms. GOLD I, IIA, IIB, based on FEV_1, with three thresholds: 80%, 50%, and 30% of predicted values. GOLD III FEV_1 <30% predicted or presence of respiratory failure or right heart failure	0: Avoid risk factors, vaccination. I: Short-acting bronchodilator (SOS) II: Regular bronchodilator + inhaled corticosteroid (*, **) + rehabilitation III: previous + oxygen? + surgery?
2006 [42]	GOLD 0 ("at risk") **disappeared**. GOLD I-IV, based on FEV_1, with three thresholds: 80%, 50%, and 30% of predicted values. GOLD IV also included those with FEV_1<50% predicted + chronic respiratory failure	I: Avoid risk factors, vaccination. Short-acting bronchodilator (SOS) II: Add Regular long-acting bronchodilator + rehabilitation III: Add inhaled corticosteroid (**) IV: Add oxygen? / Surgery?
2011 [43]	GOLD I-IV **only** based on FEV_1, with three thresholds: 80%, 50%, and 30% of predicted values GOLD A-D based on 3 binomial variables: AB vs CD: • If predicted FEV_1 >50% and Exacerbations per year <2 and none hospitalized, A-B, else C-D A/B C/D criterion: Symptoms score • If mMRC <2 or CAT <10, A or C, else B or D	anticholinergic or β_2-agonist (short-acting for A, long for B) + Inhaled corticosteroid (C or D). + Rehabilitation (B-D) Several additional alternatives choices are reported, mainly combinatory of previous.
2017 [44]	GOLD I-IV without changes (FEV_1 based) GOLD A-D based only on exacerbations history and symptoms score. (FEV_1 is now excluded from A-D)	A: SOS bronchodilator B: LAMA/LABA or LAMA+LABA (if persistent symptoms). C: LAMA or, if exacerbation, +LABA or +ICS. D: LAMA, if exacerbations, LAMA+LABA[+ICS] + macrolide? (ex-smoker) + roflumilast (if FEV_1<50% and chronic bronchitis). + Rehabilitation (B-D)

2023 [45,46]	GOLD I-IV without changes (FEV_1 based) GOLD C/D has been consolidated into a new category "E" (≥2 exacerbations or 1 hospitalized exacerbation per year); A and B remain unchanged.	A: SOS bronchodilator B: LABA+LAMA (sometimes preferred only one of them) E: LABA+LAMA, +ICS (if blood eosinophils >300), + azithromycin (ex-smoker) + roflumilast (if FEV_1<50% and chronic bronchitis). + Rehabilitation (B, E)

(*) if significant symptoms and lung function response, (**) if repeated exacerbations LAMA: long-acting muscarinic antagonist (anticholinergic); LABA: long-acting β2-agonist; SOS: a demand, when is required/ rescue treatment.

From the inception of the GOLD recommendations in **2001** until **2010**, classification focused almost exclusively on **FEV_1 thresholds**, with respiratory failure included in the most severe stage.[40,42] This element was explicitly removed in the **2011 edition**. [43] The GOLD I-IV categories have remained unchanged, although **ERS/ATS guidelines** currently recommend replacing cut-offs with **Z-scores (−1.65, −2.5, −4.0)**, as discussed earlier.[58]

The most significant shift occurred in **2011**, when **symptom criteria and frequent exacerbator status** were incorporated, substantially modifying treatment recommendations [43]. Subsequent GOLD versions simplified earlier frameworks, excluding FEV_1 from the A–D/E classification and emphasising **exacerbation history**.

Interestingly, the most recent update of **GesEPOC (2021)** ("Guía Española de la EPOC" or Spanish Guideline of COPD) employs the three criteria from the 2011 GOLD guidelines for risk classification, simplifying them into **low risk** (equivalent to 2011 GOLD A) and **high risk** (if at least one "risky" criterion is present – equivalent to 2011 GOLD B-D), while omitting the COPD Assessment Test (CAT) score. [114]

Both **GOLD** and **GesEPOC** guidelines recommended follow their **symptomatic-based classifications (GOLD A-E and low/high risk)**, which focus specially exacerbations, for the guide their treatment and management strategies.

5.1 COPD Symptomatic evaluation

Symptoms are basically evaluated using the **COPD Assessment Test (CAT)** and the **modified Medical Research Council dyspnoea scale (mMRC).** (Table 8)

Table 8 Comparison of CAT and mMRC scales for COPD symptom assessment.

Feature	COPD Assessment Test (CAT)	Modified Medical Research Council scale (mMRC)
Scope	Overall burden of COPD on daily life	Dyspnoea-related activity limitation
Format	8 self-reported items	1 self-reported item
Score range	0–40 [the worst] (each item 0–5)	0–5 [the worst]
Domains assessed	Cough, phlegm, chest tightness, dyspnoea on exertion, limitation of home activities, confidence outdoors, sleep disturbance, fatigue	Breathlessness during activities of daily living
Cut-off values in guidelines	≥10 often used to identify higher symptom burden	≥2 indicates clinically significant limitation
Strengths	Broad multidimensional evaluation; widely accepted by patients	Simple, quick to administer; widely used in research and accepted by patients
Limitations	Subjective; some overlap with mMRC (breathlessness item); requires completion of 8 items (longer)	Subjective; Focus only on dyspnoea; variability in patient interpretation (esp. grades 0, 2, 3); less sensitive to symptom change

The **CAT**, developed by the GOLD initiative, assesses the overall **burden of COPD on a patient's life**. It is a self-reported questionnaire of eight items, each scored from 0 to 5, giving a total score between 0 and 40. The evaluated domains include: cough frequency, phlegm in the chest, chest tightness, dyspnoea when climbing hills or stairs, restrictions in home activities, reduced confidence to leave home due to respiratory symptoms, disturbed sleep, and fatigue [59,115].

The **mMRC dyspnoea scale** specifically assesses **activity limitations caused by breathlessness**. It is a self-reported score ranging from 0 to 5, with a cut-off of **≥2** generally used in clinical guidelines. Grade 2 indicates limitation when walking at ground level (walking slower than peers or having to stop due to breathlessness) [116,117,59,114].

However, the use of these scales has some **limitations**. Studies have shown that CAT and mMRC scores may yield **inconsistent classifications** of patients, particularly among those with milder symptoms. This mismatch arises because the CAT captures a wider spectrum of COPD manifestations, whereas the mMRC focuses solely on exertional dyspnoea [118,119]. Moreover, significant variability has been reported in patient interpretation of mMRC descriptors, particularly at grades 0, 2, and 3, suggesting that the scale may not reliably distinguish severity or detect meaningful changes in exertional dyspnoea [120,121].

The main limitation of both instruments is their **subjective nature**, as they rely entirely on patient perception of symptom burden. Nevertheless, they both remain valuable for understanding the **impact of COPD on quality of life** and are both widely accepted by patients [122,123]. The CAT, in particular, provides broader information, although the "breathlessness when walking" item, conceptually similar to the mMRC, remains the **most discriminative component** of the test (GOLD C–D) [122] .

6 COPD Exacerbations, their relevance and effects

Since 2011, the paramount aspect in COPD therapy has been the **management of exacerbations**, particularly in **exacerbators**. Both **GOLD** and **GesEPOC** guidelines provide differentiated treatment strategies for these patients [43,59,114]. A exacerbator, according these guidelines, is defined as a patient who experiences **≥2 exacerbations per year** or **≥1 exacerbation requiring hospitalisation** [43].

6.1 Exacerbation definition(s)

The definition of an exacerbation, sometimes abbreviated as **ECOPD** and at other times **AECOPD** to refer specifically to an acute exacerbation, is not entirely clear, and several approaches have been proposed over time. As these definitions have evolved, a brief review is warranted.

The **GOLD 2011** defined it as "*an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication*". [43] This does not differ substantially from the current **GesEPOC 2021 guideline**, which re-termed the condition as **COPD exacerbation syndrome (CES)** and defined it as: "*CES is defined as an episode of clinical instability that occurs in a patient with COPD as a result of worsening of expiratory airflow limitation or the underlying inflammatory process and is characterized by an acute worsening of the individual's respiratory symptoms relative to baseline*".[124]

The main difference between these two definitions lies in the **explicit inclusion of the inflammatory process as a pathogenic mechanism** in the GesEPOC

version, although otherwise the definitions are essentially equivalent. While both are clinically useful, they retain a significant degree of **subjectivity**, complicating the precise attribution of the term 'exacerbation' to specific clinical episodes [125–127]. For instance, studies have shown that the perception of dyspnoea during CO_2 rebreathing is heightened in frequent exacerbators but diminished in infrequent exacerbators. Such discrepancies may partly explain the variability in reported exacerbation rates among patients [127]. This **heterogeneity of definition** inevitably affects clinical trials and research studies, limiting comparability, interpretation, and application of findings [128].

Previously, four common definitions of exacerbations have been also used in clinical studies of chronic obstructive pulmonary disease (COPD). [129]

1. **Three cardinal symptoms (Anthonisen criteria):** increased dyspnoea, increased sputum volume, and increased sputum purulence. Exacerbations were further classified as [129,130]:
    a. **Type I:** all three symptoms present.
    b. **Type II:** any two symptoms present.
    c. **Type III:** one symptom plus at least one of the following: upper respiratory tract infection in the last 5 days, fever of unknown origin, worsening wheeze, increased cough, or ≥20% increase in respiratory or heart rate relative to baseline
2. **Symptom pattern criteria over 2 days:** ≥2 major symptoms (as above) or one major plus one minor (nasal discharge, wheeze, sore throat, cough, or fever) over two consecutive days [131].
3. **Consensus-based clinical deterioration (used in GOLD 2011):** persistent deterioration in health status requiring a change in usual COPD therapy [43,132].
4. **Symptom persistence criteria over 3 days:** constellation of respiratory symptoms (e.g. cough, wheeze, dyspnoea, sputum production) persisting for more than three days [133].

In **2021**, a new proposal was suggested, which remains unvalidated but has been accepted, the **Rome proposal**. It states that "*in a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over =<14 d, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways*".[125]

This proposal was subsequently adopted in the **GOLD 2023 guideline**. Like its predecessors, it emphasises clinical features but also places greater focus on the **inflammatory process as a pathophysiological basis**. However, the **time restriction of ≤14 days** may limit its utility for identifying exacerbations at their earliest stages, when early intervention is known to improve outcomes [134].

Moreover, the narrowing of the definition to inflammatory events raises practical challenges, as the absence of reliable **biomarkers** restricts accurate identification and classification [135].

For these reasons, many authors argue that **biomarkers, particularly biomolecular ones, are urgently needed** to reduce the subjectivity of symptom-based definitions and to enable more reliable detection of COPD exacerbations, both in real-world clinical practice and in research settings [136,137].

6.2 Challenges in exacerbation hospitalisation criteria

The second criterion for classifying a patient as a frequent exacerbator is the occurrence of at least one exacerbation requiring hospitalisation in the preceding year. However, the definition of **hospitalisation criteria** remains inconsistent. Both the **GesEPOC 2021** [124] and the **2025 GOLD guideline** [59] provide more detailed specifications, yet important discrepancies persist. *(*Table 9*)*

Table 9 Comparison between GesEPOC and GOLD criteria for hospitalisation in AECOPD

GesEPOC 2021	2025 GOLD Guideline
No improvement after appropriate treatment and 6–12 h observation	Failure of an exacerbation to respond to initial medical management
Respiratory acidosis (pH < 7.35)	Acute respiratory failure Severe symptoms (e.g. sudden worsening of resting dyspnoea, tachypnoea, decreased O_2 saturation, confusion, drowsiness) Onset of new physical signs (e.g. cyanosis, peripheral oedema)
PaO_2 < 55 mmHg	
$PaCO_2$ > 50 mmHg in patients without previous hypercapnia	
Need for non-invasive mechanical ventilation	
Pneumonia (if meeting pneumonia severity criteria for admission)	
Serious complications or comorbidities: Pleural effusion Pneumothorax venous thromboembolism Rib fractures Cardiovascular disorders (heart failure, ischaemic heart disease, uncontrolled arrhythmias) Severe anaemia	Presence of serious comorbidities (e.g. heart failure, newly occurring arrhythmias)
Insufficient home support	Insufficient home support

Although many of these criteria are **objective**, particularly those listed in GesEPOC, others are inherently **subjective**, such as "insufficient home support." Moreover, several external factors may influence whether an exacerbation is ultimately recorded as "hospitalised." These include **administrative pressures** to reduce (or in some systems, to increase) admissions, **patient self-management capabilities**, availability of home-based outreach services, and variability in national or regional healthcare policies [137].

Additionally, factors unrelated to the clinical severity of the exacerbation may condition hospitalisation or even reporting of the event. Examples include **healthcare accessibility**, distance to the clinic, availability of transport (public or private), the patient's capacity to attend (e.g. those dependent on oxygen therapy), and the limited infrastructure for structured home-visit programmes by physicians [138]. Such considerations highlight the **limitations of using hospitalisation as the sole criterion** for defining severe exacerbations.

6.3 Exacerbation effects, recurrence, and mortality

The definition, identification, and management of exacerbations remain of paramount importance, as they represent one of the most powerful predictors of **COPD progression and mortality** [136,139,140]. This makes their prevention and control a central challenge in COPD management.

6.3.1 Effects of AECOPD on lung function, musculature, activity, and emotional status

COPD exacerbations are strongly associated with an accelerated decline in **lung function**, particularly among individuals with modest airflow limitation who experience severe exacerbations [141] Recovery of pulmonary function following an exacerbation is often incomplete: evidence suggests that in approximately **25% of cases**, lung function does not return to pre-exacerbation levels even five weeks after the event, and in around **7% of cases**, recovery remains incomplete three months later [142].

Beyond lung function, **exacerbations negatively affect multiple physiological systems**. Documented consequences include reduced **exercise capacity**, decreased **muscle strength**, diminished levels of **physical activity**, increased **daytime somnolence**, shorter **total sleep duration**, impaired **sleep efficiency**, and higher levels of **fatigue** [138].

The underlying mechanisms of **muscle loss and weakness** during exacerbations are multifactorial. Proposed contributors include **oxidative stress**, **mitochondrial dysfunction**, systemic and local **inflammation**, impaired **regenerative capacity**, increased activation of **catabolic pathways**, and even **apoptosis of muscle fibres** [143–145]. Another potential explanation is the frequent use of **prolonged systemic**

glucocorticoid therapy, which may impair the differentiation capacity of myogenic stem cells and thereby hinder recovery of muscle mass [146].

These physical limitations also restrict patients' ability to plan daily activities such as walking, sleeping, and speaking. A large international **patient survey** reported that exacerbations significantly disrupt daily life and worsen patients' outlook [147]. Moreover, exacerbations contribute to **balance deficits**, closely linked to dyspnoea and muscle weakness, which increase the risk of **falls**. Collectively, these consequences foster higher rates of **depression and anxiety** among both patients and their families, ultimately exacerbating the deterioration of **health-related quality of life (HRQoL)** [138].

6.3.2 Cardiovascular effects of COPD Exacerbation

There is growing evidence that the **pathobiological and pathophysiological effects of COPD exacerbations extend beyond the pulmonary system**, with a particularly strong impact on **cardiovascular outcomes** [148–150]. These include, but are not limited to, **myocardial infarction, stroke, heart failure decompensation, arrhythmia,** and cardiovascular-related **mortality**.

In recent years (2022–2024), attention has increasingly focused on the risk of cardiovascular events associated with COPD exacerbations. A **meta-analysis of 533,620 patients**—mostly from the UK, USA, and Northern Europe, but also including other countries—reported that within three months following an exacerbation, the relative risk (RR) of **myocardial infarction** was 2.43 (95% CI 1.40–4.20) and of **stroke** was 1.68 (95% CI 1.19–2.38) [151].

A **UK cohort study** demonstrated a three-fold increase in cardiovascular events (defined as acute coronary syndrome, arrhythmia, heart failure, ischaemic stroke, or pulmonary hypertension) within 1–14 days after an exacerbation of any severity, with the risk remaining elevated for over one year. This was most pronounced in the two weeks following a **severe exacerbation** (adjusted HR 14.5; 95% CI 12.2–17.3) and in the 14–30 days following a **moderate exacerbation** (adjusted HR 1.94; 95% CI 1.63–2.31). Extrapolation to the broader COPD population suggested that over **28% of severe exacerbations** and **22% of mild exacerbations** were followed by a cardiovascular event. Importantly, the incidence of **heart failure** remained significantly elevated throughout the median follow-up of 2.4 years (adjusted HR 2.33; 95% CI 2.24–2.42) [152].

Similar results have been reported in other cohorts. In a **Canadian study** of 142,787 patients, the adjusted HR for **heart failure** was 2.25 (95% CI 1.96–2.59) for up to 180 days after an exacerbation of any severity [153]. In the **Netherlands**, the adjusted HR ranged from 2.5 (95% CI 1.3–4.8) after moderate exacerbations to as high as 48.6 (95% CI 36.9–64.0) after severe exacerbations, for the risk of major

cardiovascular events or cardiovascular-related mortality in the first seven days post-event, with the increased risk persisting beyond one year [150,154].

Evidence from the **IMPACT trial** also supports this association: a post hoc analysis revealed that the overall risk of cardiovascular events increased during both moderate and severe exacerbations and remained elevated for 30 days, even among patients with **minimal baseline cardiovascular risk** [155]. In line with these findings, the **Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)** and the **Spanish Society of Cardiology (SEC)** jointly published in 2024 the first version of a guideline entitled *"Multidisciplinary Management of Patients with Chronic Obstructive Pulmonary Disease and Cardiovascular Disease"*, emphasising the cardiovascular dimension of COPD care [156].

In addition to major cardiovascular morbidity, many patients also report **dissatisfaction with sexual performance**, with **erectile dysfunction** being particularly prevalent among men [150]. This may be linked to cardiovascular dysfunction and hormonal alterations, although the precise mechanisms remain uncertain.

Finally, a **recent review (2024)** noted that while no studies have yet directly assessed the relationship between cardiovascular outcomes and the **frequency or severity** of exacerbations, the presence of cardiovascular disease in COPD patients is consistently associated with more frequent exacerbations, higher cardiovascular-related hospitalisation rates, and greater mortality [150].

6.3.3 Exacerbation recurrence and COPD progression

The progression of COPD can be partly explained by a **vicious cycle of exacerbations**, which may render patients housebound, exacerbate sadness, reduce physical activity, and further compromise lung function [138]. This activity restriction contributes to disease progression by reducing ventilation and impairing lung clearance [157].

Multiple risk factors have been associated with recurrent exacerbations, including persistently elevated **blood eosinophil count (BEC)**, suboptimal baseline health status, **gastro-oesophageal reflux**, bacterial colonisation of the lower airways, and chronic mucus hypersecretion [136]. Other factors include the severity of airflow limitation, radiological evidence of emphysema, advanced age, and systemic inflammation [158]. Collectively, these factors may explain why a **previous history of exacerbations remains the strongest predictor of future events**, particularly those requiring hospitalisation [158].

The underlying mechanisms of the **frequent exacerbator phenotype** are likely multifactorial, involving persistent post-exacerbation inflammation and lung

hyperinflation, both of which diminish physiological reserve and increase susceptibility to subsequent events [136].

A particularly illustrative example comes from a **large Canadian cohort study** involving 73,106 patients followed over 17 years [159] (Figure 4). This study reported three major findings:

1. The **inter-exacerbation interval** shortens progressively with each recurrence, from 5.4 years between the first and second events to fewer than four months between the ninth and tenth.
2. The **risk of a new severe exacerbation peaks in the first trimester after an event**, reaching 30–40 per 10,000 per day, before declining to a lower baseline level.
3. The **baseline rate of severe exacerbations increases cumulatively** with each recurrence, from approximately 3 per 10,000 per day at the first event to 50 per 10,000 per day by the ninth.

These data provide compelling evidence that **exacerbations not only worsen prognosis acutely** but also **accelerate long-term disease progression**, underlining the clinical importance of breaking this cycle early and reinforcing the need for prevention and early intervention.

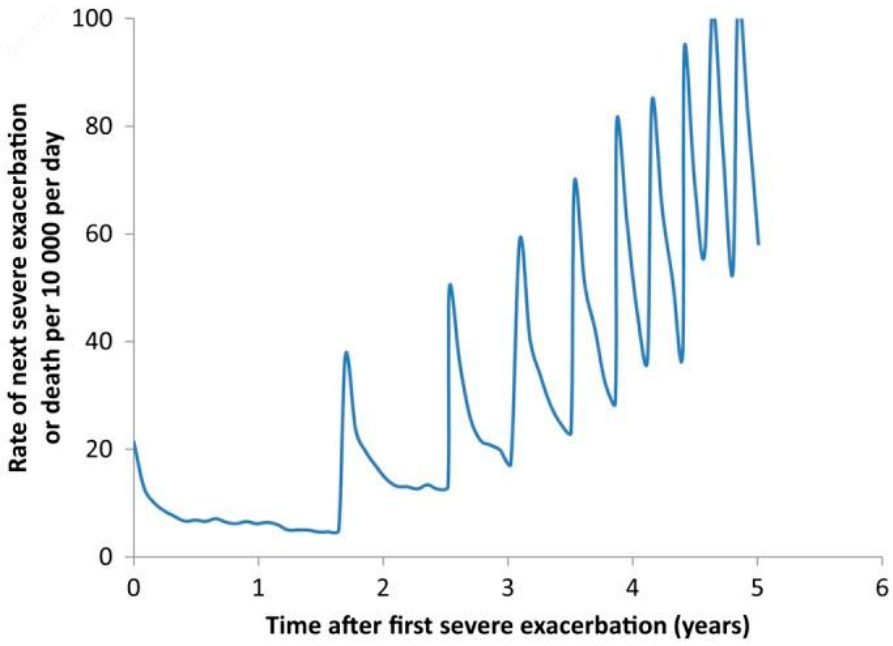

Figure 4 Temporal pattern of recurrent hospitalised COPD exacerbations
Hazard function of successive hospitalised chronic obstructive pulmonary disease (COPD) exacerbations (per 10 000 per day) for the cohort of 73 106 patients from the time of their first ever hospitalisation for a COPD exacerbation over the follow-up period, with the time between successive exacerbations estimated using the median inter-exacerbation times as time to the next exacerbation or death, whichever occurs first. Extracted from [159]

6.3.4 Mortality related to COPD exacerbation

A recent meta-analysis (2024) including 65,945 patients from studies conducted between 2000 and 2018 across Europe, Asia, and Oceania estimated an inpatient mortality rate of **6.2% worldwide** among patients hospitalised for a COPD exacerbation, with a lower rate of **3.6% in Spain.** Advanced age, the use of non-invasive or invasive mechanical ventilation (NIMV/IMV), and ICU admission were strongly associated with an increased risk of in-hospital death. Conversely, male sex and European ethnicity were associated with reduced odds of in-hospital mortality, likely reflecting differences in follow-up and healthcare systems in these populations. Notably, no association was found with classical COPD variables such as FEV_1, mMRC, prior exacerbations, or previous hospitalisations [160]

Importantly, mortality related to COPD exacerbations is not limited to acute in-hospital events. **Post-hospitalisation mortality remains strikingly high.** A Canadian cohort including 73,106 patients (1990–2005) demonstrated that deaths following a severe exacerbation peaked in the first week after discharge, with **40 deaths per 10,000 patients per day**, and only **50% of patients survived beyond 3.6 years** [159]. These findings are corroborated by recent pooled estimates: global post-hospitalisation mortality rates were **7.1% (95% CI 6.8–7.3) at 30 days**, **12.6% (95% CI 12.3–12.9) at 90 days**, and **32.1% (95% CI 31.6–32.5) at one year**. In contrast, Spain showed considerably lower values of **1.1%, 4.2%, and 5.5%**, respectively [160].

7 Mortality of COPD

Chronic Obstructive Pulmonary Disease (COPD) has been the **third leading cause of death worldwide** (excluding SARS-CoV-2–related mortality) since 1998. In 2019, COPD accounted for **3,280,636 deaths** (95% CI: 2,902,855–3,572,367), representing **5.48%** (95% CI: 4.96–5.92%) of all deaths, according to the *Global Burden of Disease (GBD) Study*. This translated into **54,594,898 years of life lost (YLLs)** (95% CI: 48,711,468–59,513,367), with an age-standardised rate of **680.8 YLLs per 100,000 inhabitants** (95% CI: 606.4–741.6) [90] Figure 5 illustrates the mortality evolution by regions and globally as well as its geographical distribution.

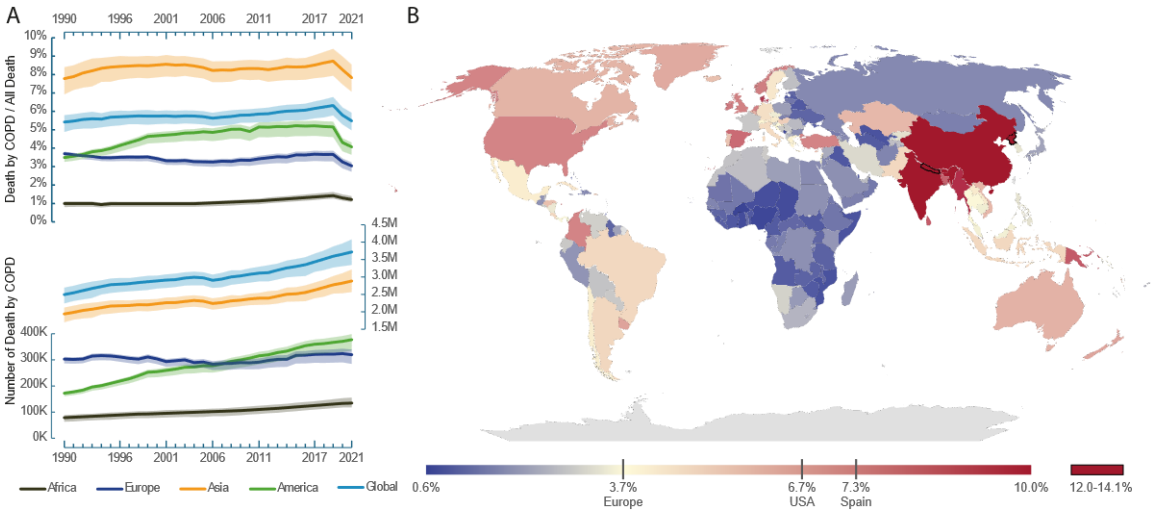

Figure 5 Evolution of COPD mortality worldwide (A) and geographical distribution (B)

The line graphs depict the temporal trend in the number of deaths attributed to COPD by region and globally, expressed as a percentage of total reported deaths (top) and as absolute numbers (bottom). Shaded areas around the lines represent 95% confidence intervals. The map shows the proportion of COPD-related deaths of all-cause mortality by country in 2019, with values ranging from 0.6% to 10% on a colour scale. Mortality percentages for Europe (3.7%), the USA (6.7%) and Spain (7.3%) are highlighted in the legend. Data from 2020 and 2021 were excluded due to the confounding impact of the COVID-19 pandemic. Countries exceeding the scale's upper limit by >2% are outlined in black. Abbreviations: M, million; K, thousand. Based on data from the *Global Burden of Disease Study* [87].

An accompanying publication from the GBD collaborators underlined that, although the **absolute number of COPD deaths has risen** due to demographic expansion and ageing, **age-adjusted mortality rates have declined steadily**, showing a **41.7% reduction** (95% CI: 47.6–32.2) between 1990 and 2019 [90]. This paradox reflects improvements in prevention and management, particularly in high- and middle-income countries (including Spain), partially offset by persistent risk factors in low-income settings.

The *GBD Study* is a cornerstone in the COPD literature [90,161,162]; however, it may **underestimate mortality rates**. Notably, countries with the **highest levels of underdiagnosis** (Figure 2) tend to overlap with those reporting **lower mortality ratios** (Figure 5), suggesting that true COPD-related mortality is likely higher than reported.

In Spain, COPD ranks among the **leading causes of death**. For example, in 2011, it was the **fourth leading cause** nationwide. More recently, positive trends have been observed. A study analysing age-adjusted COPD mortality based on data from the Ministry of Health statistics portal (1999–2019) [161] demonstrated a **marked reduction**: from nearly **29 deaths per 100,000 inhabitants** in the late 1990s to approximately **12 deaths per 100,000 inhabitants** two decades later. This reduction was seen in both sexes but with distinct trajectories:

- **Men:** higher baseline mortality, with a consistent linear annual decrease of −3.67% (95% CI: −4.1 to −3.4).
- **Women:** a sharper initial decline between 1999–2006 (−6.8% per year; 95% CI: −8.6 to −5.0), followed by a slower but sustained decline thereafter (−2.1% per year; 95% CI: −2.8 to −1.3).

This indicates **sex- and region-specific differences** in risk exposure and healthcare management, warranting further analysis to guide improvements.

Current estimates suggest COPD causes **11,000–18,000 deaths annually in Spain**. Nevertheless, mortality may be **substantially underestimated**, as COPD is frequently omitted as the primary cause of death certificates, often being replaced by conditions such as pneumonia or heart failure, despite COPD being the underlying driver [161]. Furthermore, the **high underdiagnosis rates in Spain** (74.7%, see Section 4.2) reinforce the likelihood that official mortality statistics underrepresent the true burden.

7.1 Mortality prediction

As mentioned earlier, the degree of lung involvement and the functional consequences of COPD are critical prognostic factors. Historically, the **forced expiratory volume in one second (FEV_1)** has been regarded as a predictor of mortality, since a diminished FEV_1 correlates with increased risk of death [24,25,28,39]. Patients with very low FEV_1 (<50% of predicted, equivalent to GOLD stages 3–4) were believed to have markedly reduced 5-year survival rates [40]. However, **FEV_1 alone does not fully capture the heterogeneity of COPD**, as individuals with identical values may have markedly different prognoses. This limitation motivated the development of multidimensional prognostic scores.

7.1.1 Multidimensional indices

The overall **functional status of the patient**—including exercise ability, muscle strength, and nutritional condition—has been shown to be strongly linked to mortality. Regardless of lung function, **low body mass or weight loss (particularly cachexia)** is associated with a worse prognosis [144,163]. Similarly, **chronic dyspnoea**, when objectively assessed (mMRC grades 4–5), is a powerful risk marker; indeed, studies demonstrate that the dyspnoea score alone can stratify survival in COPD almost as effectively as FEV_1 [164,165]. These observations underscore that **COPD is a systemic and functional condition**, not merely confined to pulmonary impairment, and justify the development of multidimensional indices.

One of the most widely used tools is the **BODE index** (*Body mass index, Obstruction, Dyspnoea, Exercise capacity*), proposed by Celli et al. (2004). It integrates four variables: body mass index (BMI), FEV_1 (% predicted), dyspnoea (measured with the mMRC scale), and distance walked in the 6-minute walk test (6MWT). Scores range from 0 to 10, with higher values indicating worse prognosis. In its first validation trial with 625 patients, each 1-point increase was associated with a **34% increase in all-cause mortality (HR 1.34)** and a **62% increase in respiratory mortality (HR 1.62)** [166].

Some variants of BODE have been developed [167]:

- **e-BODE**, incorporating exacerbation history (with minimal additional predictive capacity).
- **BODEx**, substituting 6MWT with exacerbation frequency, making it more feasible for primary care.

Another widely used score is the **ADO index** (Age, Dyspnoea, Obstruction), designed for simplified application in primary care [168]. ADO appears to outperform BODE in predicting **1-, 5-, and 10-year mortality**, although this advantage diminishes when BODE variants are adjusted for age [169]. This highlights **age itself as main predictor of death**, which is expected given the association of advanced age with COPD comorbidities and outcomes. A proposed variant, the **CADOT index**, incorporates chronic heart failure and the transfer factor for carbon monoxide (TLCO). However, TLCO measurement is more challenging to perform than the six-minute walk test (6MWT), and CADOT requires further validation, as only a two-year follow-up is currently available [170]. In any case, CADOT represents an attempt to integrate **non-pulmonary factors** into prognostic assessment.

7.1.2 Comorbidity burden

In addition to **age**, certain **comorbidities** are frequently observed among individuals with **COPD**, including **cardiovascular disease**, **metabolic disorders**,

osteoporosis, **muscle weakness**, **anxiety and depression**, **cognitive decline**, and other **respiratory conditions**, all of which have important implications for the **prognosis** and **management** of COPD. These comorbidities may compromise **quality of life** (e.g., asthma, anxiety/depression, muscle dysfunction, cognitive decline), obscure the **diagnosis of COPD** owing to **non-specific symptoms** (e.g., cardiovascular disease, obesity, other pulmonary conditions), or substantially increase the risk of **exacerbations** (asthma, anxiety/depression, gastro-oesophageal reflux disease, bronchiectasis, cardiovascular disease) and **mortality** (anxiety/depression, bronchiectasis, cardiovascular disease). Despite the considerable influence of comorbidities on disease outcomes, **no specific clinical guidelines** currently exist for the **identification, assessment, or management** of comorbidities in patients with COPD [165].

Charlson Comorbidity Index (CCI), also referred to simply as the **Charlson Index**, is widely employed in **clinical practice** to evaluate the burden of **comorbidities**. It encompasses a range of conditions, including: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, liver disease (mild or moderate/severe), diabetes (controlled or uncontrolled), hemiplegia or paraplegia, renal disease, malignancy (localised or metastatic), leukaemia, lymphoma, and AIDS. [171,172]

Further adaptations of the **BODE index** have incorporated the evaluation of **comorbidities**. The **CODEX index** (*Comorbidity, Obstruction, Dyspnoea, Exacerbation*) was developed for this purpose, employing the **Charlson Index** to account for comorbid conditions. It is conceptually similar to **BODEx**, but substitutes **BMI** with the **Charlson Index** [173,174]. More recently, a modified version, the **mCODEX**, has been introduced, with revised cut-off values derived from **survival prediction analyses** in the **3CIA cohort** and the **ADO index**. This modification demonstrated improved accuracy for **short-term prognostic predictions (<1 year)**, although it did not show superiority in **long-term outcomes** [175].

An enhanced approach was the development of the **COPD-specific Comorbidity Test (COTE)**, designed to evaluate the **prognostic impact** of selected comorbidities. This index includes **COPD-related comorbidities**, such as **anxiety** (in women), **diabetes with neuropathy**, **liver cirrhosis**, **gastric or duodenal ulcer disease**, **pulmonary fibrosis**, and various forms of **cancer** (including lung, oesophageal, pancreatic, breast, and others), together with **cardiovascular conditions** such as **atrial fibrillation/flutter**, **coronary artery disease**, and **congestive heart failure**. This test has also demonstrated robust performance in predicting **mortality**, independently of the **BODE index** [176].

7.1.3 Mortality performance of COPD indices

A range of multidimensional indices have been developed. Their predictive performance is summarised in Table 10.

Table 10 Multidimensional indices for COPD: components and validation for mortality prediction

Index	Components	Sensitivity	Specificity
BODE [166]	**B**MI, airflow **O**bstruction, **D**yspnoea, **E**xercise capacity	5y: 82.81 10y: 70.27 [177]	5y: 70.75 10y: 89.93 [177]
e-BODE [167]	**e**xacerbation + **B**MI, airflow **O**bstruction, **D**yspnoea, **E**xercise capacity	5y: 87.50 10y: 73.87 [177]	5y: 69.81 10y: 89.83 [177]
BODEx [167]	**B**MI, airflow **O**bstruction, **D**yspnoea, **Ex**acerbation	5y: 75.00 10y: 66.67 [177]	5y: 66.04 10y: 83.05 [177]
Charlson Comorbidity Index (CCI) [171,172]	General Comorbidity	5y: 73.44 10y: 68.47 [177]	5y: 59.43 10y: 76.27 [177]
CODEX [173,174]	**C**omorbidity (CCI), airflow **O**bstruction, **D**yspnoea, **Ex**acerbation	5y: 85.94 10y: 63.96 [177]	5y: 57.55 10y: 94.92 [177]
COmorbidity TEst (COTE) [176]	COPD-specific Comorbidity	5y: 73.44 10y: 66.67 [177]	5y: 64.15 10y: 81.36 [177]
ADO [168]	**A**ge, **D**yspnoea, airflow **O**bstruction	5y: 84.37 10y: 54.95 [177]	5y: 58.43 10y: 96.61 [177]
CADOT	**C**hronic heart failure, **A**ge, **D**yspnoea, airflow **O**bstruction, **T**LCO	NA (External validated at 2y, only C-statistics provided: 0.84)	
VAPORED [178]	**V**ital capacity, **A**ge, **P**neumonia, airflow **O**bstruction ratio, **R**esting SatO2 (%), **D**yspnoea.	NA (External validated at 3y, only AUC provided: 0.73)	
ABEODS [179]	**A**ge, **B**MI, **E**ducational level, airflow **O**bstruction, **D**yspnoea, **S**evere exacerbation	NA (External validated at 3y, only AUC provided: 0.80)	
FODEP [180]	**F**at-free mass index, airflow **O**bstruction, **D**yspnoea, **E**xercise capacity, maximal inspiratory **P**ressure	2y: 81.25	2y: 76.45

Abbreviation: NA, No Available; y, Years

Their main value of these indices lies in capturing the **systemic and multidimensional nature of COPD**, thereby enabling more reliable risk stratification for both clinical management and research purposes. However, although these indices substantially improve prognostic accuracy compared with FEV_1 alone, their **predictive capacity remains moderate**, and **none directly addresses the underlying pathobiology** of COPD. In this regard, predictive biomarkers remain promising candidates to enhance prognostic assessment in the future.

8 Personalised medicine and biomarkers in COPD

The lack of significant improvements in COPD treatment outcomes has shifted the focus from traditional "one-size-fits-all" medicine toward precision and personalised medicine. (Figure 6)

8.1 General concepts of personalised medicine

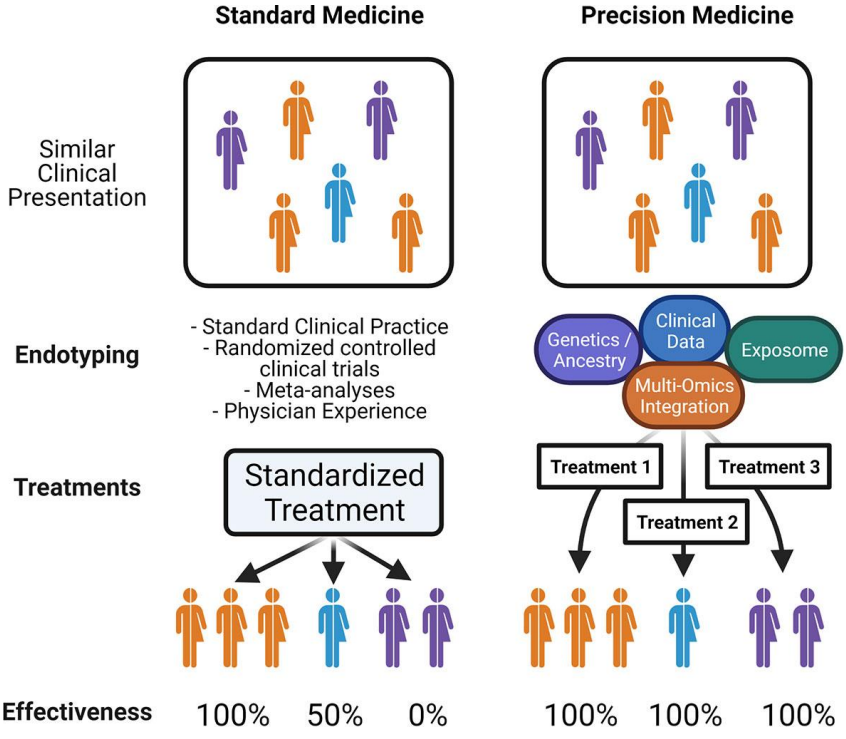

Figure 6 Comparison between standard medicine and precision medicine
Extracted from [181]

To address the inherent heterogeneity of COPD, several biological approaches have been proposed, particularly the use of **clinical phenotypes, endotypes, biomarkers, and, more recently, treatable traits**.

The concept of **phenotype** was first defined in 1909 by Wilhelm Johannsen, who distinguished between the inherited provisions of organisms (genotype) and the observable manifestations of those provisions (phenotype) [182]. A phenotype can thus be defined as "*the state of an organism resulting from interactions between genes, environment, disease, molecular mechanisms, and chance*" [183] That should encompass mostly all clinical symptoms and signs, obstruction pattern in spirometry, exacerbation, fever, classical blue bloaters and pink puffers, but also observable characteristics that can be measured in the laboratory [184], as an elevation of eosinophils.

By contrast, an **endotype** refers to a disease subtype defined by a distinct pathobiological mechanism and/or aetiology [183,185]. Consequently, endotypes are more closely associated with the biological background of the patients. Importantly, multiple endotypes may present within the same phenotype (Figure 7). [181]

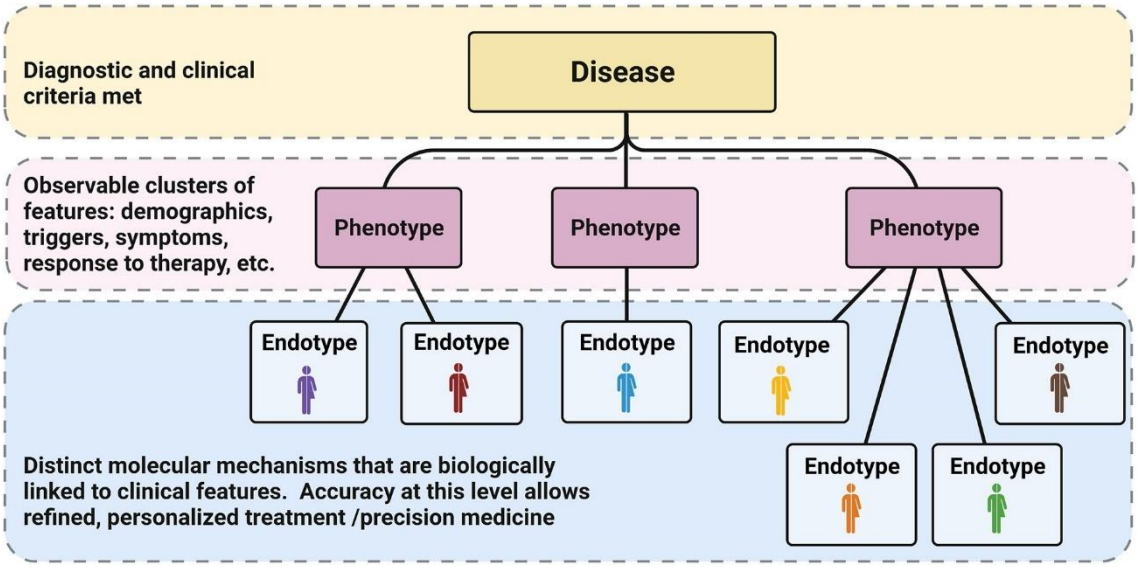

Figure 7 Graphical distinction of Disease Phenotype and Endotype in general clinical medicine and biology

Extracted from [181]

Following those definitions, a "clinical phenotype" should be a phenotype with practical clinical relevance, i.e., attributes that help guide prognosis, treatment, or disease management. [183]

8.2 Adaptation of personalised medicine concepts to COPD

Nonetheless, in COPD context those concepts differ. A clinical phenotype is "*a single or combination of disease attributes that describe differences between individuals with [the same disease] as they relate to clinically meaningful outcomes*" [186] A rigid reading of this definition led some authors to understand that clinical phenotypes

are **mutually exclusive**, when it is evident that COPD oftens exhibit several combinations of no-exclusive traits. [187]

To overcome this limitation, the concept of **treatable traits** emerged. These are therapeutic targets identified through phenotypes or endotypes and supported by validated biomarker(s). Moreover, by definition, treatable traits are **clinically relevant, identifiable, and treatable**, but also **allowing mutual overlapping**. [187,188] Those can be ordered into three domains: pulmonary, extrapulmonary and risk factor/behavioural traits.

Ideally, as mentioned, each treatable trait should be identifiable by at least one **biomarker**, defined as *"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention"* [189]. Biomarkers are not limited to molecules; they may also include functional markers or imaging findings [187,188].

A schematic view of these concepts in COPD is shown in Figure 8.

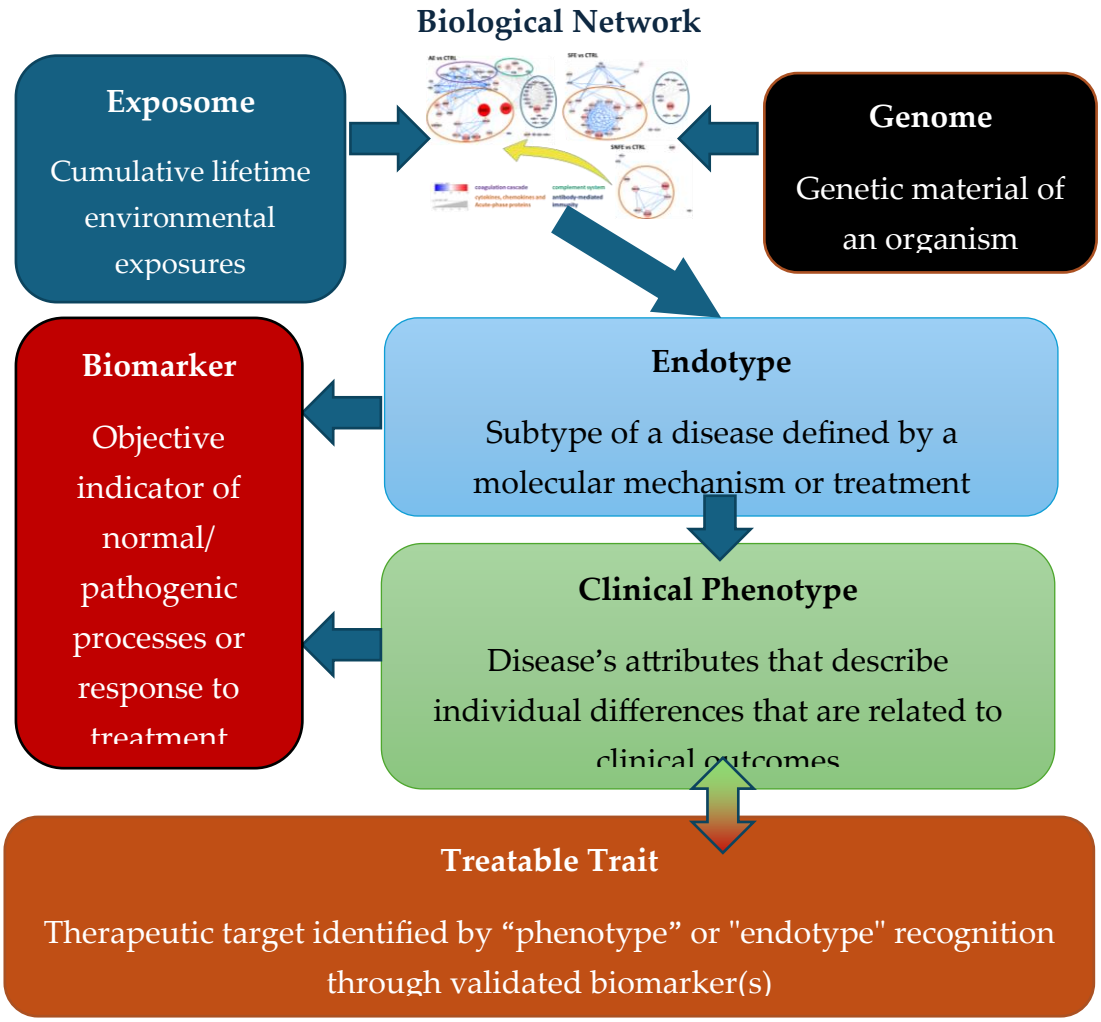

Figure 8 Schematic view of the relationships and definitions in COPD between the exposome and the genome (via complex biological networks), the endotypes and phenotypes, biomarkers and treatable traits

Based on [188]

8.3 Current Biomarkers in COPD

Several serum biomarkers have been evaluated for their diagnostic, phenotyping, and prognostic potential in COPD cohorts. However, up to the start of this thesis, attempts to identify robust biological markers had not yielded the desired results in COPD. Numerous studies have explored a small number of molecules, usually guided by pre-existing hypotheses related to inflammation, oxidative stress, tissue injury, or remodeling. Some relevant candidates investigated include **C-reactive protein (CRP), fibrinogen, pro-inflammatory cytokines, complement activation markers, lipopolysaccharide-binding protein (LBP), and adhesion molecules**, among others [59,190–193]. (Table 11)

Table 11 Biomarkers studied in COPD, classified by sample type and level of evidence

Sample Type	Readily Available and Currently Used Biomarkers	Extensively Investigated Biomarkers but Not Sufficiently Validated	Less Investigated Biomarkers
Peripheral Blood (plasma/ serum)	Eosinophils CRP Fibrinogen	MDA GSH, GSH-Px, SOD IL-6, TNFα, MCP-1	Vitamins A, E, and C GGT vWF Extracellular vesicles (CD62E+, CD31+)
Exhaled air	FeNO		Ethane
Sputum		IL-6, IL-8, TNF-α MPO MMP-8, MMP-9, MMP-12, neutrophil elastase, Eosinophil peroxidase	8-isoprostane MDA SOD, GSH-Px Leptin
Exhaled breath condensate		8-isoprostane H_2O_2	MDA IL-8
Bronchoalveolar lavage fluid		Glutathione	EGFR, HSA, A1AT, TIMP1, IL-8 and Calprotectin
Urine			8-isoprostane

Adapted and updated from [192]. *MDA: Malondialdehyde, GSH: glutathione, GSH-Px: glutathione peroxidase, SOD: superoxide dismutase, GGT: γ-glutamyltransferase, CRP: C-reactive protein, IL: interleukin, TNF-α: tumor necrosis factor-alpha, MCP-1: monocyte chemoattractant protein-1, vWF: von Willebrand factor, FeNO: fraction of exhaled nitric oxide, MPO: myeloperoxidase, MMP: matrix metalloproteinase, EGFR: epidermal growth factor receptor, HSA: human serum albumin, A1AT: alpha-1-antitrypsin, TIMP1: tissue inhibitor matrix metalloproteinase 1.*

These findings may provide valuable insights into the clinical and biological heterogeneity of COPD and contribute to the development of more personalised approaches to patient evaluation and management.

However, the **current evidence remains inconsistent**. Reported associations are highly variable, often poorly reproducible, and generally insufficient to establish definitive links with clinically relevant outcomes. Most studies were based on relatively large cohorts but designed to test specific disease circumstances (e.g., exacerbation frequency, progression speed) without subsequent external validation.

Larger initiatives, such as the **ECLIPSE study** (in which members of our group have also participated), confirmed that several systemic inflammatory markers—notably IL-6 and CRP—improve prediction of clinical outcomes [194]

Attempts to apply **omics-based approaches** in the same direction have been limited by small sample sizes or poor clinical integration [195,196]. Furthermore, non-hypothesis-driven omics studies, while promising, often revert to post hoc comparisons of predefined clinical groups. This non-blinded methodology reduces their capacity to generate prospective biomarkers and limits their translational utility [197–199].

At present, **no single blood biomarker** (except eosinophils, CRP, fibrinogen, and FeNO) **has shown sufficient performance for definitive clinical application in COPD**[192,198,200]. Consequently, there remains a clear need for rigorously validated serum/plasma biomarkers in COPD, underscoring the importance of continuing exploratory and integrative research in this field.

9 Conclusions

1. **A paradigm shift from anatomical-clinical to functional.**

   This report shows that COPD has evolved from anatomical-clinical descriptions of emphysema and chronic bronchitis to a modern definition that recognises its clinical and biological heterogeneity, but which is dependent on spirometry and functional testing. The consolidation of GOLD and, more recently, the revision promoted in 2022–2023 (included by GOLD) emphasise symptoms, structure and pathophysiology (airways/alveoli), introduce the notion of pre-COPD and dilute the etiological centrality of 'smoke/noxious substances' as a defining feature, opening the door to multiple causal pathways (genetics, abnormal lung development, infections, biomass, asthma, mixed exposures). This conceptual evolution reflects a paradigm shift towards a more functional, syndromic definition.

2. **Spirometry remains necessary, but is not sufficient.**

   Post-bronchodilator spirometry remains the recommended diagnostic confirmation criterion; although its use is insufficient, controversial thresholds (fixed FEV_1/FVC ratio 0.70 vs. LLN z-score), technical/interpretative difficulties and patient effort limitations compromise sensitivity and specificity, especially at extreme ages and in primary care settings. Alternative metrics and complementary contributions (e.g., quantitative CT imaging, functional MRI) are useful for characterising phenotypes, but they do not replace spirometry and, at present, do not systematically guide treatment.

3. **The magnitude of the diagnostic problem is structural.**

   Beyond its high prevalence, COPD suffers from massive underdiagnosis (≈87.5% in the global summary of the report), late diagnosis (years of missed opportunities) and significant overdiagnosis in primary care. The estimated confusion matrix illustrates that, globally, healthcare sensitivity is low and the accuracy of the 'COPD' label is modest; in Spain, specificity is high, but sensitivity remains limited, with the consequent clinical (delayed or inadequate treatment), economic (hospitalisations, use of resources) and human (quality of life) costs. Reducing these imbalances requires simultaneous intervention in diagnostic capacity, processes, training and access.

4. **Exacerbations are the focus of severity and management.**

   Since 2011, the 'exacerbator' phenotype has structured therapeutic stratification. The recent 'Rome' definition, adopted by GOLD, seeks to objectify the event, but it still coexists with heterogeneous thresholds and hospitalisation criteria that depend on the healthcare context and resources. Exacerbations accelerate the decline in FEV_1, cause loss of muscle mass/strength and reduce activity and sleep; they also markedly increase cardiovascular risk (coronary syndromes, heart failure, arrhythmias, stroke) in early and sustained windows after the episode. Secondary prevention of exacerbations should incorporate proactive cardiovascular strategies and coordination between pulmonology and cardiology.

5. **Mortality and prognosis: usefulness and limitations of indices.**

   COPD is one of the leading causes of death. Although age-adjusted rates tend to decline, absolute mortality remains high and is likely underestimated due to underdiagnosis. Multidimensional indices (BODE, ADO, BODEx, CODEX, COTE) outperform FEV_1 alone and capture the burden of comorbidities, dyspnoea and functional capacity; however, their performance is moderate, and they do not, on their own, guide interventions that modify the biology of the disease. Other potential predictors (including molecular ones) need to be studied in combination with comprehensive assessment, control of comorbidities, and prevention of exacerbations, beyond FEV_1 value.

6. **Biomarkers and personalised medicine: promise still unfulfilled.**

   Current evidence does not support a single blood biomarker with sufficient performance for diagnosis, phenotyping, and prognosis in routine clinical practice. The 'treatable traits' approach (pulmonary, extrapulmonary, and risk/behavioural) offers a useful clinical framework but requires validated biomarkers and multi-omic platforms with rigorous design and validation criteria, together with well-phenotyped and longitudinal cohorts. Although progress has been made, more advanced personalisation requires additional evidence.

7. A new biological definition of COPD needs to be considered.

Extending the definition of COPD to a syndromic approach has clear clinical advantages, as it supports simplicity and practicality in daily management. However, this has led to greater biological heterogeneity intrinsic to the breadth of the definition and the need to manage treatable risks (not unlike syndromic management), like the strategy used in fever syndrome, where obstruction is one more curable aspect. In this context, it is important to ask whether we should return to anatomical-clinical definitions as a strategy for studying COPD in a more biological-molecular, objective and clear manner, in parallel to keep the current definition for clinical practice.

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11 Appendix

11.1 Appendix 1

Extraction translated from [15]:

> *Observation XX: 'De vesiculis pulmonalibus obstructis et ab aeris occlusionis expansis.'*
>
> *In one part of the lung, I found a cluster of transparent vesicles, expanded by air and so obstructed that I could not empty them of air with slight compression. I found that when air was applied through the trachea, there was no communication with these expanded vesicles due to their obstruction. Then, by forcing air through the trachea with force, some of these vesicles ruptured. Others, pierced with the tip of a needle, released air and deflated.*
>
> *In 1685, in the presence of His Excellency Dr Sylvio and Master Heyunga, well versed in the art of surgery, I performed the dissection of the corpse of a merchant who had suffered from dyspnoea for a long time, accompanied by coughing and continuous fever. See Figure 20.*
>
> *This condition worsened significantly after he fell into the water, to the point that, over time, he could barely breathe. In fact, he died not long after.*
>
> *During the opening of the corpse, we observed that the entire problem lay in a blocked part of the lung, where all the vesicles appeared blocked and distended, as can be seen in Figure 21.*

11.2 Appendix 2

Extraction translated from [17]:

Book I, section II, observation LVII. § Apoplexia citò interimens, cerebro omnino salvo et incolumi, solo vitio in Pulmonibus apparente.

> *the lungs were discoloured and foamy with ichor everywhere, clearly revealing the cause of the heart attack, difficult and labored breathing.*

Detailed column 'Pulmones discolorés & ichore spumoso &c.' (p.126):

> **Hippocrates explains which parts are affected in this disease. In his work 'De morb.', book 6, he mentions: This occurs when black bile is activated and flows, mainly to the part where there are more veins, such as the neck and chest. Subsequently, the patient becomes weak and loses functional capacity because the blood, when cooled, coagulates. The brain is also affected, being deprived of vital spirits, which is clearly deduced from the impotence and abolition of animal functions.*
>
> *Snoring and difficulty breathing also depend on this same coagulation of the blood, as Hippocrates observed in cases of severe apoplexy, in which there is great difficulty in breathing. Swollen veins are detected in the neck, which led him to correctly infer that the capillary veins of the lungs were obstructed. This caused the blood, impeded in its circulation, to stagnate in the jugular veins and expand the larger veins of the lungs. As a result, the bronchi narrow, preventing sufficient air from entering in cases of extreme need for breath, unless the thorax expands significantly, as moderate expansion is not enough to fill the cavity.*
>
> *This shows that in severe apoplexy, the lungs are affected, and their blood vessels are obstructed.*

11.3 Appendix 3

Here is explained the formulas used for **deriving standard diagnostic performance metrics** (Sensitivity, Specificity, Positive Predictive Value [PPV], Negative Predictive Value [NPV], Accuracy, and Matthews Correlation Coefficient [MCC]) **from population prevalence (π), underdiagnosis (U), and overdiagnosis (O_A).**

All rates were treated as unitarian proportions (0 to 1).

11.3.1 Symbols and definitions

- N: total population size (useful only for confusion matrix reconstruction).
- π: prevalence of COPD in the target population.
- U: underdiagnosis rate = $\frac{FN}{(TP+FN)}$, proportion of true COPD cases not diagnosed (among all true COPD).
- O_A: overdiagnosis rate among diagnosed cases = $\frac{FP}{(TP+FP)}$, in our case, spirometric discarded diagnosis/ COPD initially diagnosed

11.3.2 Reconstruction of the confusion matrix

- True COPD $= \pi \cdot N = TP + FN$
- Non-COPD $= (1-\pi) \cdot N = TN + FP$
- $TP = (1-U) \cdot \pi \cdot N$
- $FN = U \cdot \pi \cdot N$
- $FP = \frac{O_A}{1-O_A} \cdot TP = \frac{O_A}{1-O_A} \cdot (1-U) \cdot \pi \cdot N$
- $TN = (1-\pi) \cdot N - FP = (1-\pi) \cdot N - \frac{O_A}{1-O_A} \cdot (1-U) \cdot \pi \cdot N$

11.3.3 Diagnostic metrics

- Sensitivity $= \frac{TP}{TP+FN} = 1-U$
- Specificity $= \frac{TN}{TN+FP} = 1 - \frac{\frac{O_A}{1-O_A} \cdot (1-U) \cdot \pi}{1-\pi}$
- PPV $= \frac{TP}{TP+FP} = 1 - O_A$
- NPV $= \frac{TN}{TN+FN} = \frac{(1-\pi) - \frac{O_A}{1-O_A} \cdot (1-U) \cdot \pi}{(1-\pi) - \frac{O_A}{1-O_A} \cdot (1-U) \cdot \pi + U \cdot \pi}$
- Accuracy $= \frac{TP+TN}{N} = 1 - (U \cdot \pi) - \frac{O_A}{1-O_A} \cdot (1-U) \cdot \pi$
- MCC $= \frac{TP \cdot TN - FP \cdot FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}} = \frac{\pi(1-U) \cdot \left[(1-\pi) - \frac{O_A \pi(1-U)}{1-O_A}\right] - \frac{O_A \pi(1-U)}{1-O_A} \pi U}{\sqrt{\left(\pi(1-U) + \frac{O_A \pi(1-U)}{1-O_A}\right) \cdot \pi \cdot (1-\pi) \cdot \left((1-\pi) + \pi(1-U)\right)}}$

Note that N is not necessary required to calculate diagnostic metrics.