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Chronic obstructive pulmonary disease: exacerbations and mortality

Prognostic value of biomarkers and comorbidities

JENS ELLINGSEN



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Abstract

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Background: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. COPD is associated with systemic inflammation, and comorbidities are common. A characteristic feature is acute exacerbations (AECOPDs), i.e., episodes of worsening symptoms. AECOPDs are associated with increased mortality.

Aim: To find prognostic risk factors for COPD mortality and AECOPDs, focusing on comorbidities and inflammatory biomarkers.

Methods: In Paper I, associations between comorbidities, pharmacological treatment, and mortality were analysed in a real-world cohort of almost 18,000 primary care COPD patients. Data from medical records and national registers were analysed in Cox proportional hazards regressions.

Papers II–IV were based on the Tools Identifying Exacerbations (TIE) cohort study of 572 COPD patients recruited from primary and secondary care in three Swedish regions. Participants were invited to three yearly visits, including phlebotomy, spirometry, and health questionnaires.

In Paper II, the ability of blood neutrophil-to-lymphocyte ratio (NLR) and eosinophils (B-Eos) to predict AECOPDs was analysed with mixed-effects logistic regressions.

In Paper III, the ability of C-reactive protein (CRP), fibrinogen, blood leukocytes (B-Leu), and four blood cell indices to predict AECOPDs was analysed with ordinal logistic regressions.

In Paper IV, an algorithm for clinical phenotyping previously developed to predict mortality was studied. The algorithm's ability to predict AECOPDs and mortality was analysed with Cox proportional hazards regressions; additionally, the identified phenotypes were analysed concerning differences in blood-based inflammatory biomarkers.

Results: Several comorbidities, including heart diseases, were associated with increased mortality risk. Some pharmacological treatments were associated with increased or decreased mortality risk (Paper I). NLR, B-Eos, CRP, fibrinogen, and B-Leu (Papers II–III) predicted AECOPDs after adjustment for confounders, whereas other blood cell indices were of limited value (Paper III). The clinical phenotyping algorithm predicted AECOPDs and mortality, and the phenotypes had different patterns of inflammatory biomarkers (Paper IV).

Conclusions: Comorbidities, particularly heart diseases, are substantial risk factors for mortality in COPD and should be an integral part of management of COPD patients. NLR, B-Eos, CRP, fibrinogen, and B-Leu are independent predictors of AECOPDs and should be further investigated as parts of, e.g., risk prediction tools. A previously developed algorithm for clinical phenotyping predicts mortality and AECOPDs.

Keywords: COPD, exacerbations, mortality, biomarkers, comorbidity

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It is difficult to make predictions, especially about the future.
Unknown

List of Papers

This thesis is based on the following papers, referred to in the text by their Roman numerals.

- I. Ellingsen J, Johansson G, Larsson K, Lisspers K, Malinovski A, Ställberg B, Thuresson M, Janson C. Impact of Comorbidities and Commonly Used Drugs on Mortality in COPD – Real-World Data from a Primary Care Setting. *Int J Chron Obstruct Pulmon Dis*. 2020;15:235-45.
- II. Ellingsen J, Janson C, Bröms K, Lisspers K, Ställberg B, Högman M, Malinovski A. Neutrophil-to-lymphocyte ratio, blood eosinophils and COPD exacerbations: a cohort study. *ERJ Open Res*. 2021;7(4):00471-2021.
- III. Ellingsen J, Janson C, Bröms K, Hårdstedt M, Högman M, Lisspers K, Palm A, Ställberg B, Malinovski A. CRP, fibrinogen, leukocytes, and blood cell indices as prognostic biomarkers of future COPD exacerbation frequency: the TIE cohort study. (submitted)
- IV. Ellingsen J, Janson C, Bröms K, Farkhooy A, Hårdstedt M, Högman M, Lisspers K, Palm A, Ställberg B, Malinovski A. Clinical phenotypes predict exacerbations of COPD: the TIE cohort study. (manuscript)

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Abbreviations

ACCEPT	Acute COPD Exacerbation Prediction Tool
AECOPD	acute exacerbation of COPD
aHR	adjusted hazard ratio
ACEi	angiotensin-converting enzyme inhibitor
AISI	aggregate index of systemic inflammation
aOR	adjusted odds ratio
ARB	angiotensin-II receptor blocker
ASA	acetylsalicylic acid
B-Bas	blood basophils
B-Eos	blood eosinophils
B-Leu	blood leukocytes
B-Lym	blood lymphocytes
B-Mon	blood monocytes
B-Neu	blood neutrophils
B-Plt	blood platelets
BMI	body mass index
CAT	COPD Assessment Test
CCI	Charlson Comorbidity Index
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
FDA	Food and Drug Administration
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
GERD	gastro-oesophageal reflux disease
GOLD	Global initiative for Chronic Obstructive Lung Disease
HF	heart failure
HR	hazard ratio
ICC	intraclass correlation coefficient
ICD-10	International Classification of Diseases, 10 th revision
ICS	inhaled corticosteroids
IHD	ischaemic heart disease
IQR	interquartile range
LABA	inhaled long-acting beta-2-agonist

LAMA	inhaled long-acting muscarinic antagonist
LLN	lower limit of normal
MI	myocardial infarction
mMRC	modified Medical Research Council dyspnoea scale
NAC	N-acetylcysteine
NLR	neutrophil-to-lymphocyte ratio
OCS	oral corticosteroids
OR	odds ratio
PLR	platelet-to-lymphocyte ratio
PRISm	preserved ratio, impaired spirometry
RCT	randomised controlled trial
SD	standard deviation
SII	systemic immune-inflammation index
SIRI	systemic inflammation response index
SSRI	selective serotonin reuptake inhibitor
SVC	slow vital capacity
TIE	Tools Identifying Exacerbations in COPD
V/Q	ventilation-perfusion

1 Introduction

1.1 The history of COPD

The term *chronic obstructive pulmonary disease* was coined in 1965,¹ but the existence of the disease was known long before.² What was later called emphysema (from the Greek for inflation) was described in autopsy reports already in the late 17th century, and the first known illustrations were published by Ruysch in 1691.³ Several descriptions of voluminous, non-emptying lungs with vesicles or blebs were published in the 18th century, but it was René Laënnec who, in publications from 1819 and onward, described the disease and formed the foundation for our pathophysiological understanding of it.⁴ He realised that emphysema was rather common and recognised that several cases previously described as nervous asthma – asthma was at the time a symptom rather than a diagnosis³ – were actually emphysema. In a description of an autopsy, Laënnec also noted a case of chronic bronchitis, although the term was not coined at the time.² The first known clinical description of chronic bronchitis – then referred to as *catarrh* – had been published by Charles Badham a few years earlier (1814).² The spirometer was invented in the mid-19th century, but it was not until the mid-20th century that the typical findings of airflow obstruction on spirometry were described.²

It was also in the mid-20th century that awareness of the disease that would later be coined chronic obstructive pulmonary disease (COPD) started to grow in the medical community. Around 1960, definitions of chronic bronchitis and emphysema were established by the American Thoracic Society.² Chronic bronchitis was defined as a productive chronic cough lasting for at least three months within a period of two years. Emphysema was defined based on patho-anatomical findings, i.e., enlarged alveolar spaces and loss of alveolar walls. These definitions are still in use. In the 1960s, the concept of a disease with chronic airflow obstruction characterised by emphysema and/or chronic bronchitis evolved, and several names circulated before *COPD* became established.^{1,2} Treatments were developed and studied, with the first inhalation treatments emerging in the early 1960s and long-term oxygen later that decade.² Lung volume reduction surgery was first described in 1957.⁵

Beginning in the 1960s, the knowledge of the pathology of COPD grew significantly, thanks to the first experimental models of emphysema and, in part, the Swedish discovery of alpha-1 antitrypsin deficiency.^{2,6} During the 1970s, the role of smoking as a major cause of COPD was uncovered, with

Charles Fletcher as a key contributor.⁷ In the following decades, the importance of smoking cessation was established in the landmark Lung Health Study, which showed benefits regarding lung function decline and mortality.^{8,9} In the 1990s, the heavy impact of COPD in terms of morbidity, mortality, and healthcare costs was increasingly recognised, and large-scale initiatives to improve lung health through, e.g., early detection and smoking cessation interventions, were launched.¹⁰ A milestone was the formation of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in the early 2000s.¹¹ This also led to the establishment of the diagnostic criteria where the airflow obstruction of COPD is confirmed through spirometry and defined as a ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) < 0.7.¹¹ With some modifications, those diagnostic criteria are still upheld by GOLD.¹²

1.2 Defining COPD

The current definition according to GOLD 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.¹²

It was first introduced in the GOLD 2023 report.^{13,14} The definition has been changed several times over the years, but the key components of airflow limitation, chronic bronchitis, and emphysema – recognised in the 1960s – have always been part of it.

Table 1. Subgroups of chronic obstructive pulmonary disease (COPD).¹²

Term	Meaning
COPD	Symptoms and history consistent with COPD and FEV ₁ /FVC < 0.7 after bronchodilation.
Early COPD	Pathobiological early COPD, regardless of the patient's age.
Young COPD	COPD in a patient < 50 years old.
Mild COPD	COPD with mild airflow obstruction, i.e., FEV ₁ > 80% of predicted.
Pre-COPD	Clinical, radiological, or other findings suggestive of COPD, but FEV ₁ /FVC ≥ 0.7.
PRISm	Preserved ratio, impaired spirometry, i.e., FEV ₁ /FVC ≥ 0.7, but FEV ₁ < 80% of predicted.

Abbreviations: FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

A few subgroups acknowledged by GOLD deserve mention (Table 1).¹³ *Early COPD* refers to the first pathobiological steps and should not be confused with *young COPD*, i.e., COPD afflicting someone < 50 years old. Moreover, it

should not be confused with *mild COPD*, as mild refers to the degree of airflow obstruction. *Pre-COPD* is used for patients with symptoms, radiological features (e.g., emphysema) and/or other findings suggestive of COPD but without airflow obstruction on spirometry. *PRISm* is an acronym for ‘preserved ratio, impaired spirometry’ used for patients with an $FEV_1/FVC > 0.7$ but $FEV_1 < 80\%$ predicted. There is insufficient evidence on how these subgroups should be managed; accordingly, subgroups have little impact on daily practice.

1.3 Aetiology and risk factors

As stated in the definition above, COPD is a heterogeneous disease. The heterogeneity applies to both its origins and its clinical presentation. The latter is discussed in section 1.5 Clinical presentation below. Regarding its aetiology, the dominating and most well-known cause of COPD is exposure to tobacco smoke, damaging the airways and alveoli, which leads to a lung function decline that is faster than the physiological decline seen in all ageing adults.^{7,15-17} The disease can also be caused by inhalation of other lung irritants, including through air pollution, occupational exposures, and household biomass fuel combustion,¹⁵⁻¹⁹ the latter occurring particularly in low- and middle-income countries. However, exposure alone is not a sufficient cause, illustrated by the fact that not all smokers develop COPD.²⁰ Environmental factors interact with the intrinsic factors of those exposed. Intrinsic factors include age, where the risk of COPD increases with higher age,¹⁵ and genetics, where alpha-1 antitrypsin deficiency is the best characterised – but not only – genetic cause of susceptibility to lung-toxic substances.²¹

The prevalence of COPD differs between male and female individuals,²² but whether the risk of developing COPD also differs between sexes is under debate; there is some evidence suggesting that females are more susceptible to noxious inhalations.²³ Moreover, there is an increasing awareness that impaired lung development during gestation, childhood, or adolescence increases the risk of COPD.^{24,25} Factors influencing lung development include maternal smoking, birth-weight, and infections.^{24,26-28} In these cases, the predisposition for COPD is thought not to be related to accelerated decline of lung function but rather to a failure to reach maximal possible lung function and a resulting earlier drop into obstruction than those who reach their predicted peak.²⁵ Furthermore, infections in adulthood may increase the risk of COPD,²⁹ and long-lasting asthma may cause chronic airflow obstruction.

Although asthma with non-reversible airflow obstruction is generally considered a differential diagnosis to COPD,¹² there is evidence that some never-smoking asthma patients develop features of COPD, e.g., emphysema.³⁰ The relationship between asthma and COPD has been a topic of significant debate in the last decade, and there is no reason to believe that the score is settled yet.

A significant reason for GOLD's 2023 update to the COPD definition,¹³ initially proposed by Celli *et al.* 2022,¹⁴ was to underscore that smoking is not the only aetiology of the disease. GOLD proposes the term *etiotype* for COPD of differing aetiologies: genetic factors – COPD-G; abnormal lung development in childhood and youth – COPD-D; cigarette smoking – COPD-C; exposure to air pollution including biomass smoke – COPD-P; infections – COPD-I; asthma – COPD-A; unknown causes – COPD-U.¹³ These etiotypes have no practical implication on COPD management today but serve as a reminder of the different pathways leading to disease and a common platform for future research.

1.4 Pathology and pathophysiology

There are two principal components of COPD – airway disease and emphysema – whose respective contributions to the disease vary between patients. The common denominator is a complex inflammatory process, though this also varies between patients.³¹ Inhalation of noxious gases and particles causes local airway epithelium inflammation, dominated by macrophages, neutrophils, and lymphocytes, and with oxidative stress as a key mediator.³¹ Disturbances in the airway microbiome may also be involved.³² Through poorly understood mechanisms, the inflammation becomes self-perpetuating (i.e., it continues even if the inhalational irritant is removed) and chronic. The inflammatory cells involved gain certain characteristics distinguishing them from normal cells, i.e., they become dysfunctional.^{31,33}

The chronic inflammation has devastating effects on the lungs. In the airways, especially the bronchioles, chronic bronchitis/bronchiolitis leads to mucosa swelling, smooth muscle hypercontractility, and increased mucus production, all contributing to the narrowing of the lumen (Figure 1, Figure 2).^{34,35} With time, structural changes occur in and around the airways, including squamous metaplasia of the epithelium, peribronchiolar fibrosis, smooth muscle hypertrophy, and vascular abnormalities such as intimal and smooth muscle hyperplasia.^{31,34-37} Destruction of elastin and other connective tissue components by proteases released by inflammatory cells in turn leads to the destruction of small airways and alveolar walls, which results in loss of elastic recoil of the lungs and is thought to be the primary pathobiological mechanism causing emphysema.^{33,38} The inflammation in the lung also affects pulmonary blood vessels, particularly arterioles, where intimal hyperplasia, endothelial dysfunction, and blood vessel remodelling may lead to pulmonary hypertension.³⁶

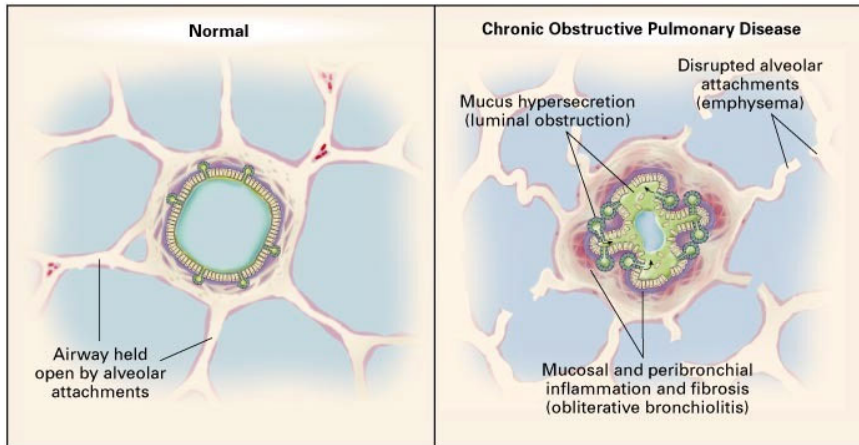


Figure 1. Schematic illustration of the processes leading to airflow limitation in COPD. Reproduced with permission from Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med.* Jul 27 2000;343(4):269-80, Copyright Massachusetts Medical Society.

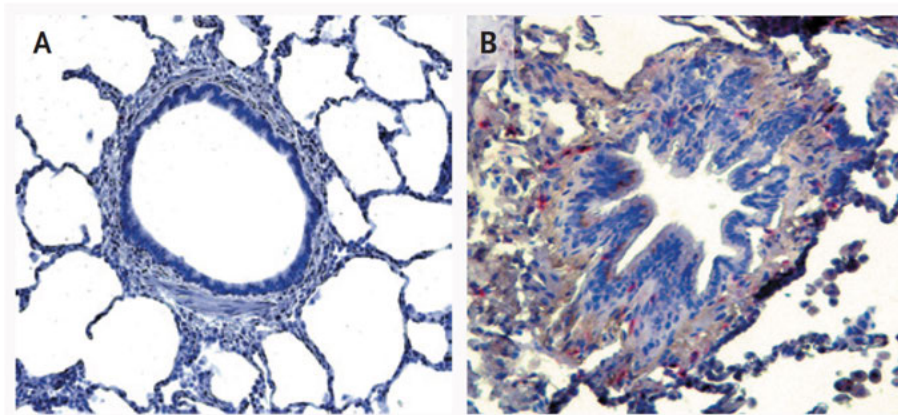


Figure 2. Histological samples from the lungs of a healthy non-smoker (A) and a smoker with COPD (B) showing sections of bronchioles with surrounding parenchyma. A. The airway walls are thin, and intact alveoli are attached along its circumference. B. The diameter of the airway is narrowed, the airway wall is thickened, and many of the alveolar attachments are broken. Images courtesy of Dr Fiorella Calabrese. Reproduced with permission from Cosio MG, Saetta M, Agustí A. Immunologic aspects of chronic obstructive pulmonary disease. *N Engl J Med.* Jun 4 2009;360(23):2445-54, Copyright Massachusetts Medical Society.

The narrowed lumen of the small airways, along with loss of alveolar attachments and elastic recoil due to emphysema (Figure 1, Figure 2), leads to airflow limitation, which manifests primarily as difficulty exhaling, i.e., emptying the lungs.^{35,39} Airflow limitation, with poorly ventilated parts of the lungs,

contributes to ventilation-perfusion (V/Q) mismatch, which increases the ventilatory demand, i.e., the patient has to breathe more to maintain normal gas exchange because of the V/Q mismatch.⁴⁰ Also, emphysema *per se*, where alveoli are lost and the total lung area contributing to the gas exchange is diminished, results in increased dead space and V/Q mismatch.

The mechanisms leading to airflow limitation may also lead to *hyperinflation* of the lungs – also called *air trapping* – when they are not entirely emptied during expiration, i.e., when the end-expiratory volume increases.⁴¹ Hyperinflation may result in a distended thorax (clinically referred to as ‘barrel chest’), where inspiratory muscles become functionally weakened and the chest wall mechanics become abnormal.⁴⁰ This contributes to a decreased ability to increase ventilation when the ventilatory need increases. Because of the hyperinflation, breathing is close to the total lung capacity, i.e., breaths become shallower and less efficient. In other words, the ratio of dead space to tidal volume increases.⁴⁰ Hyperinflation is a significant cause of dyspnoea in COPD.⁴¹ It may be static, but is usually dynamic, which means that it increases when ventilation increases, e.g., during exertion, with worsening of dyspnoea as a consequence.³⁹

Dyspnoea in COPD is multifactorial, complex, and not fully understood. The current paradigm is that dyspnoea results from an imbalance between the inspiratory neural drive to breathe and the respiratory system’s response to that drive.⁴⁰ The drive to breathe is increased by hypoxaemia, hypercapnia, and acidosis, all of which can be caused by airflow limitation, emphysema, and the associated V/Q mismatch. The normal response to such stimuli is increasing ventilation, i.e., breathing more. In COPD, hyperinflation, the V/Q mismatch, and increased physiological dead space reduce the efficiency of the ventilatory response. Malnutrition, sarcopenia, and depression may contribute to dyspnoea, mechanistically or psychologically.⁴⁰ Pulmonary hypertension as a complication in COPD will increase dyspnoea,³⁶ as may several comorbidities, most notably heart failure (HF).

COPD is associated with systemic inflammation, i.e., higher levels of blood-based inflammatory biomarkers than in healthy non-smokers.⁴² The reason for the systemic inflammation in COPD is not fully understood. It was believed that the pulmonary inflammation ‘leaked’ to the rest of the body, but that theory has been rejected.⁴³ Other theories include that systemic inflammation is a concurrent pathobiological process in COPD or that some comorbidity associated with systemic inflammation, such as obesity, may be the reason.³¹ The effects of smoking, lung hyperinflation, and hypoxia may be other sources of systemic inflammation.⁴⁴ Regardless of its cause, systemic inflammation is thought to contribute to the extrapulmonary effects of COPD, such as sarcopenia and comorbidities, including heart diseases.^{31,44}

1.5 Clinical presentation

COPD is heterogeneous, as is its clinical presentation. It is characterised by non-specific symptoms, most notably dyspnoea and cough with or without sputum production.^{45,46} Dyspnoea is usually chronic and progressive, worsens upon exertion, and causes disability.⁴⁵⁻⁴⁷ Exertion intolerance is common. Patients may adapt to their symptoms; by avoiding exertion, for instance, they avoid dyspnoea. This may pose a challenge to the clinician as a patient might not say that they are troubled by dyspnoea.

Fatigue is another common symptom that contributes significantly to disability.⁴⁸ Wheezing might be present, especially during exertion, and may be audible to the patient or only to a healthcare provider during auscultation.^{12,49} With increasing disease severity, symptoms such as weight loss and sarcopenia become more common.^{50,51} Symptoms might also arise from comorbidities such as osteoporosis, heart disease, depression, or anxiety.^{52,53}

1.6 Epidemiology

COPD is a common condition estimated to affect about 7% of adults living in Sweden.¹⁵ It is estimated by the Global Burden of Disease study that about 212 million people globally are living with COPD.¹⁷ Fortunately, the prevalence of COPD is decreasing worldwide, partly thanks to tobacco control programmes and improved housing, i.e., reduced indoor air pollution.^{15,17} However, such prevalence data must be interpreted cautiously. They heavily depend on the chosen definition of COPD, how the diagnosis is ascertained, and how the prevalence is measured. Studies using diagnosis codes from healthcare systems or registers cannot ensure that the diagnoses are correct; they will miss those who remain undiagnosed, and low access to healthcare in some areas may bias the results. Studies using population-based samples of invited participants to estimate the entire population's prevalence depend on the sample being representative of the population, and rigorous confirmation of COPD through, for instance, spirometry may lead to overdiagnosis of clinically insignificant cases.

1.7 Diagnosing COPD

COPD is a clinical diagnosis, i.e., a physician must consider the facts and determine if the diagnosis should be established (Figure 3). There is no single test to rule in COPD, although a spirometry to confirm non-reversible airflow obstruction ($FEV_1/FVC < 0.7$) is required by GOLD and in current Swedish guidelines.^{12,54} An important caveat is that non-reversible airflow obstruction is not specific to COPD; several other conditions, including asthma, can yield

the same result. Besides spirometry, the diagnostic process involves a thorough history with an assessment of symptoms and risk factors suggestive of COPD, as reviewed in previous sections. If any of the spirometry, symptoms, or risk factors do not fit well with COPD, one should hesitate to make the diagnosis. In addition, differential diagnoses must always be considered, including asthma, lung cancer, HF, and several others.

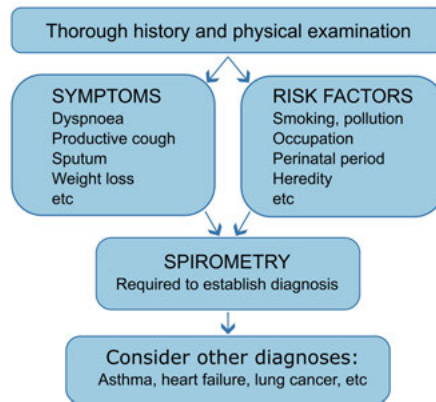


Figure 3. Diagnosing COPD, schematic illustration. COPD is a clinical diagnosis, requiring consideration of symptoms, risk factors, spirometry, and differential diagnoses.

Using a fixed FEV_1/FVC ratio to define airflow obstruction has some limitations. The most important is that it is an arbitrary cut-off not based on physiological data. Indeed, there are champions of an alternative approach where, instead of the < 0.7 limit, reference values based on spirometry studies are used, and the FEV_1/FVC ratio is related to a reference for patient age, sex, and height, similar to how FEV_1 and numerous other respiratory physiological measures are assessed. In this scenario, the lower boundary of the reference interval (referred to as the *lower limit of normal*, LLN) of FEV_1/FVC is used to define airflow obstruction, rather than the fixed < 0.7 ratio. The LLN is higher than 0.7 for younger people and lower than 0.7 for older people. The interpretation is that the fixed ratio underdiagnoses airflow obstruction in younger people and overdiagnoses it in older people.⁵⁵

Another limitation of the FEV_1/FVC ratio is the use of the FVC. During a forced manoeuvre, the pressure exerted by the respiratory musculature may cause the transpulmonary pressure to exceed the airway pressure and result in collapse of the airway. This is referred to as *dynamic compression*.⁵⁶ The dynamic compression will cause air trapping, i.e., increased end-expiratory lung volume compared with that achieved during a slow (unforced) manoeuvre. On the spirometry report, the higher end-expiratory volume will translate to a lower FVC than the slow vital capacity (SVC) and an FEV_1/FVC higher than

the FEV₁/SVC. In other words, using only FEV₁/FVC may lead to cases of airflow obstruction being erroneously classified as normal.⁵⁷

Despite these limitations, the fixed FEV₁/FVC ratio is upheld.¹² The main reasons are the simplicity of the FVC – performing an SVC is demanding and time-consuming for the spirometry staff – and that the < 0.7 limit is established through a plethora of scientific papers and among healthcare providers. Still, clinicians must be aware of the fixed ratio’s limitations, again underscoring that COPD is a clinical, not a spirometry, diagnosis.

1.7.1 Severity grades and risk groups

When a diagnosis of COPD is established, the subsequent steps are to assess the severity of airflow obstruction, the symptoms, and the risk of acute exacerbations (AECOPDs).^{12,54} The severity of airflow obstruction is assessed through FEV₁ (per cent predicted) after bronchodilation (Table 2). Impaired FEV₁ is prognostic of several adverse outcomes, including AECOPD and mortality.^{58,59}

Table 2. The severity of airflow obstruction, GOLD grades 1–4.

Grade	Alternate denomination	FEV₁ % predicted after bronchodilation
GOLD 1	Mild	≥ 80%
GOLD 2	Moderate	≥ 50%, < 80%
GOLD 3	Severe	≥ 30%, < 50%
GOLD 4	Very severe	< 30%

Abbreviations: GOLD, Global initiative for Chronic Obstructive Lung Disease; FEV₁, forced expiratory volume in one second.

Because of the wide range of symptoms reported by COPD patients, the assessment should rely on validated multidimensional tools, e.g., the COPD Assessment Test (CAT) or the Clinical COPD Questionnaire.^{12,60} The CAT is probably the most used of these, in part because it is included in the graphics disseminated by GOLD.¹² Greater complexity in questionnaires, as seen in the St. George’s Respiratory Questionnaire, makes them less suitable for clinical use. The CAT is an eight-item scale with pairs of opposing statements on symptoms, such as ‘I never cough – I cough all the time’. The patient scores each such pair of statements 0–5, where a higher number corresponds to worse symptoms. The total CAT score goes from 0 to 40, and a score ≥ 10 is considered a high burden of symptoms.¹²

Another validated tool that is widely used – thanks to its simplicity – is the modified Medical Research Council dyspnoea scale (mMRC).⁶¹ This tool consists of statements on dyspnoea, where patients are expected to choose the statement that best matches how much dyspnoea they have, on a scale 0–4 (best–worst). A score ≥ 2 is considered a high degree of dyspnoea.¹² This score

is not multidimensional, as it considers dyspnoea only; therefore, the CAT is preferred over the mMRC.

The primary tool for evaluating a patient's AECOPD risk is to assess yearly AECOPD history. Patients with ≤ 1 AECOPD not requiring hospitalisation per year have lower risk than those with more and those hospitalised due to AECOPD. The score from the symptom assessment and the AECOPD history are then combined in a matrix to allocate the patient to GOLD group A, B, or E (Table 3). The groups are used as a basis for choice on initial pharmacological treatment.

Table 3. GOLD groups A, B, and E, based on AECOPD history and symptoms.

Exacerbation history (number per year)	Symptoms	
	A	B
≥ 2 AECOPDs, or ≥ 1 leading to hospitalisation	E	
< 2 AECOPDs, none leading to hospitalisation	CAT < 10 and mMRC < 2	CAT ≥ 10 or mMRC ≥ 2

Abbreviations: GOLD, Global initiative for Chronic Obstructive Lung Disease; AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; mMRC, modified Medical Research Council dyspnoea scale.

1.7.2 Other considerations at the time of diagnosis

Beyond allocating the patient to a grade and a group, several other parameters need the clinician's attention once a COPD diagnosis has been made.^{12,54} Here, only the most critical aspects will be discussed briefly.

Pulse oximetry should be used to find patients with hypoxaemia. An exercise test, e.g., the six-minute walking test, should be considered to identify those in greatest need of physiotherapy and at highest risk of adverse outcomes. Height and weight should be obtained. Weight loss should always be asked about. The presence of comorbidities should be assessed, in particular, lung cancer, heart diseases, malnutrition, anxiety/depression, and osteoporosis. A radiological examination of the thorax should be performed, primarily to find concurrent lung cancer. A side note is that in several areas of the world, but not Sweden, many patients with COPD qualify for lung cancer screening programmes with, e.g., yearly computed tomography scans.

Blood samples may be considered for the analysis of:

- ❖ Blood eosinophils (B-Eos), in cases where inhaled corticosteroids are considered (see next section, 1.8 Management of COPD).⁵⁴
- ❖ N-terminal pro-brain natriuretic peptide, if HF is suspected.

- ❖ Alpha-1 antitrypsin, if deficiency is suspected, for instance, in a young patient with pronounced emphysema, a patient with no significant exposure history (e.g., a never-smoker), or if there is a significant family history of COPD with pulmonary emphysema.

1.8 Management of COPD

After a thorough initial assessment, the clinician has to decide on treatment, in cooperation with the patient. The patient should then be followed up regularly.^{12,54} The frequency of the follow-up visits depends on the severity of COPD, mainly in terms of symptoms and the number of AECOPDs. At each visit, a thorough assessment is to be made, considering the aforementioned factors, to decide on any changes to the treatment regime. In the following, a brief overview will be given of the main principles of COPD treatment based on current international policies and Swedish guidelines.^{12,54}

There are two main goals of COPD treatment. The first is to improve the patient's quality of life by relieving symptoms and increasing their ability to participate in everyday activities. The second is to improve the patient's prognosis by preventing lung function impairment, AECOPDs, and mortality. Among patients not very troubled by symptoms, it may be a pedagogical challenge for the physician to convince them to adhere to a preventive treatment regime despite not experiencing immediate benefits. There are both non-pharmacological and pharmacological treatment options.

The most crucial non-pharmacological treatment is smoking cessation (with pharmacological aids if needed), which has a proven effect on, e.g., lung function decline and mortality.^{8,9} In analogy, when possible, efforts should be made to remove other exposures to agents causing pulmonary damage. Other essential interventions include patient education, a written self-management plan, nutritional support, and encouragement of physical activity and when indicated, pulmonary rehabilitation with a physiotherapist.

The principal components of pharmacological treatment are long-acting bronchodilators: long-acting beta-2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), alone or in combination. Both drug classes improve FEV₁, mitigate symptoms, and prevent AECOPDs, although neither has any proven effect on mortality. For patients with recurrent AECOPDs, a history of asthma, or B-Eos $\geq 0.3 \times 10^9$ cells/L, the addition of inhaled corticosteroids (ICS) to LABA+LAMA (triple inhaled therapy) should be considered. Triple inhaled therapy is superior to LABA+LAMA regarding FEV₁, symptoms, and prevention of AECOPD. Additionally, it reduces mortality among symptomatic COPD patients with frequent AECOPDs (further discussed in section 1.11 Mortality in COPD below).

People with COPD should receive vaccinations against airway pathogens; in Sweden, recommended vaccines for patients with COPD are those against

seasonal influenza, pneumococci, COVID-19, and respiratory syncytial virus (in patients > 60 years old). Other treatments to consider in selected patients include roflumilast, long-term antibiotics (azithromycin or erythromycin), and long-term oxygen treatment. GOLD suggests that methylxanthines (e.g., theophylline) and mucolytic agents such as N-acetylcysteine (NAC) can be used, but Swedish recommendations do not endorse these drugs. Continuous treatment with oral corticosteroids (OCS) is harmful and should not be used in COPD, although OCS have a place in the treatment of AECOPDs.

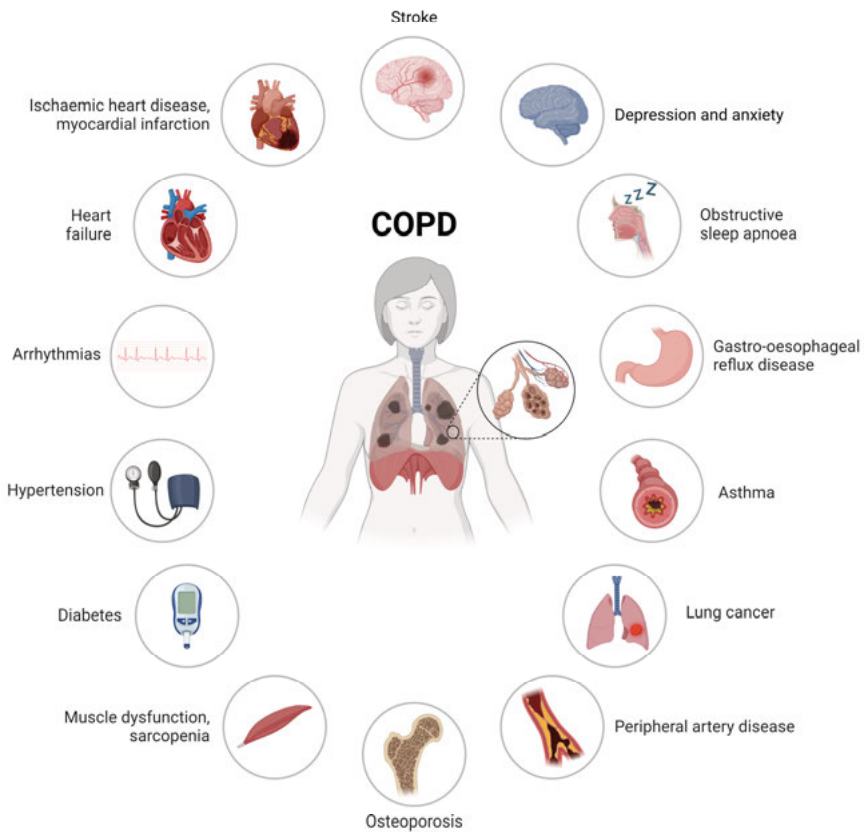


Figure 4. Common comorbidities of chronic obstructive pulmonary disease (COPD). The list is not exhaustive. Created with BioRender.com.

1.9 Comorbidities

Comorbid diseases are more common in COPD than in healthy matched controls,⁶²⁻⁶⁶ and the more severe the COPD, the more comorbidities.⁶³ The most important comorbidities are probably lung cancer and heart diseases such as HF, ischaemic heart disease (IHD), and arrhythmias, as failure to detect them

early can be deleterious (Figure 4). Other common comorbidities include hypertension, peripheral artery disease, stroke, depression, anxiety, osteoporosis, muscle dysfunction, diabetes, cognitive impairment, gastro-oesophageal reflux disease (GERD), bronchiectasis, obstructive sleep apnoea, and asthma.

There are several reasons why comorbidities are common in COPD: 1) common risk factors such as tobacco smoke, air pollution, and age; 2) systemic inflammation as a feature of COPD; 3) physiological features of COPD, e.g., hyperinflation influencing cardiac function; and 4) consequences of COPD, such as reduced physical activity and sedentary lifestyle, weight loss, or sarcopenia, increasing the risk of other conditions.^{67,68}

Besides causing more symptoms, decreased quality of life, and lower physical capacity,⁶⁹ several comorbidities seem to influence the prognosis of COPD. Asthma, bronchiectasis, GERD, HF, and others are associated with increased risk of AECOPDs,^{58,70-72} and diseases such as HF, IHD, lung cancer, stroke, diabetes, depression/anxiety, and others are associated with increased mortality.^{52,63,66,73-76} There is a cumulative effect, such that a higher number and severity of comorbidities, i.e., more severe multimorbidity, increase mortality risk.⁷³ The multimorbidity can be assessed with the Charlson Comorbidity Index (CCI), for instance. The CCI was developed in the 1980s to predict mortality in unselected populations in epidemiological studies.⁷⁷ In the CCI, individuals are assigned points for each of the comorbidities included in the index, where conditions conferring higher risk give more points.⁷⁷ The points are added up to yield a total score; the higher the score, the higher the risk of 10-year mortality. A COPD-specific comorbidity index called COTE has been developed.⁷³ However, its value has been questioned,⁷⁸ and it is not widely used. Beyond the individual suffering, comorbidities contribute significantly to the healthcare expenditures associated with COPD.⁷⁹

A common comorbidity with a debated, but probably less detrimental, association with COPD is asthma. There is evidence that concurrent asthma increases the risk of AECOPD.⁵⁸ On the other hand, studies suggest that comorbid asthma decreases COPD mortality,⁸⁰⁻⁸² although there are conflicting results.^{83,84} Different study populations and diagnostic difficulties may explain the heterogeneity across studies. GOLD acknowledges that non-reversible airflow obstruction (i.e., FEV₁/FVC ratio < 0.7 after bronchodilation) is not specific to COPD but may be found in other diseases, such as asthma,¹³ and every pulmonologist knows that the diagnoses are not always easy to distinguish. The relationship between COPD and asthma has been debated for several years, and various terminologies have been proposed, such as the *asthma-COPD overlap syndrome*,⁸⁵ no longer endorsed by GOLD.¹³ As discussed above, reports suggest that patients with asthma may develop characteristics of COPD,³⁰ and in its 2023 report, GOLD proposes the etiotype COPD-A as a term for COPD due to asthma.¹³ In summary, the relationship between asthma and COPD has not yet been fully investigated.

1.10 Acute exacerbations of COPD

A prominent feature of COPD is acute exacerbations (AECOPDs), i.e., episodes of acute worsening or flare-ups. More than two centuries ago, Laënnec recognised AECOPDs as acute episodes of worsening, frequently associated with newly developed and/or worsening cough and sputum, although he used the term *acute catarrh*.^{4,86} In its 2023 report, GOLD defined an AECOPD as

[...] an event characterized by increased dyspnea and/or cough and sputum that worsens in < 14 days which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways.¹³

Several other definitions have been used over the years.⁸⁶⁻⁹² For a long time, the most prevalent definition was *an acute worsening of respiratory symptoms that results in additional therapy*.⁸⁸ This definition has been widely used in research as it makes it possible to identify AECOPDs from drug usage data. Notably, results when studying AECOPDs will differ depending on the definition chosen.⁹²

AECOPD severity is classified *post-factum* as mild, moderate, or severe, depending on the level of treatment.¹² Mild events are treated with bronchodilators only, moderate ones with oral steroids and/or antibiotics, and severe events require hospitalisation. This definition of severity is practical for research purposes but is of no help to the clinician needing guidance on managing an acutely ill patient. Therefore, more clinically useful severity gradings have been proposed.^{54,86}

AECOPDs are deleterious, with significant, negative impacts on the course of the disease. Those with more AECOPDs have lower quality of life than those with fewer AECOPDs.⁹³ Moreover, AECOPDs accelerate lung function decline,⁹⁴ decrease cardiovascular health,⁹⁵ and increase mortality.^{96,97} The sequelae of AECOPDs are additive: the more AECOPDs a patient suffers, the worse the consequences are.⁹⁸ There is also a risk of a negative spiral as AECOPDs *per se*, and many of their consequences, increase the risk of future AECOPDs.⁹⁹ To increase awareness of the gravity of AECOPDs, some authors have proposed other names, such as *lung-attack*, with an obvious analogy to the cardiological counterpart.^{90,92}

AECOPDs are thought to arise due to an increase in airway inflammation, which is most commonly induced by a viral or bacterial infection, but there are also other causes, such as air pollution.⁹⁰ The increased inflammation worsens expiratory airflow limitation through mucosal oedema, mucus secretion, and increased smooth muscle constriction, which leads to exaggerated dynamic hyperinflation.¹⁰⁰ The dynamic hyperinflation is further increased by tachypnoea, putatively caused by dyspnoea or the inflammation itself, leading to a vicious circle of air trapping in the lungs, respiratory muscle dysfunction

due to increased elastic loading, and worsening dyspnoea.¹⁰⁰ V/Q mismatch often arises or worsens due to increased airflow limitation, leading to impaired gas exchange and respiratory failure manifesting as hypoxaemia and/or hypercapnia, further exacerbating the vicious circle.¹⁰¹

The inflammatory process during AECOPDs is heterogeneous and only partially understood. Four clusters have been proposed based mainly on inflammatory profile in sputum: neutrophilic, eosinophilic, viral-associated and pauci-inflammatory.^{102,103} It should be noted that these clusters are clinically indistinguishable.

Not all COPD patients suffer from AECOPDs; some rarely have one,¹⁰⁴ and others have them frequently, i.e., ≥ 2 per year, referred to as the frequent exacerbator phenotype.¹⁰⁵ Numerous risk factors of future AECOPDs have been described, of which the strongest is previous AECOPDs.^{58,99} Other include higher age, poor lung function, worse dyspnoea, chronic bronchitis, comorbidities such as asthma, bronchiectasis, HF, and GERD, and environmental exposures such as air pollution.^{58,70-72,106,107} Several biomarkers have been studied as predictors of AECOPDs (further reviewed in section 1.14 Biomarkers below),¹⁰⁸ but none is recommended by current guidelines.

1.10.1 Clinical presentation and management of AECOPDs

The most prominent symptom associated with AECOPDs is increased dyspnoea.¹⁰⁹ Others include increased cough, with or without increased and/or discoloured sputum, and wheezing.¹⁰⁹ Symptoms related to the cause of the AECOPD might also be present, e.g. nasal congestion in case of viral infection, as well as symptoms associated with complications of AECOPDs, e.g. respiratory failure. Symptoms may develop suddenly or gradually within two weeks.¹¹⁰ Hypoxaemia and hypercapnia may develop.

The work-up of a suspected AECOPD starts with a careful history and clinical examination.^{12,54} The clinician must know that several other potentially fatal conditions may mimic, trigger, or co-occur with an AECOPD. Such diseases include myocardial infarction (MI), HF, cardiac arrhythmias, pulmonary embolism, pneumothorax, asthma, pneumonia, etc. In addition to a clinical examination aiming to discover such conditions, measurements should be made of heart rate, respiratory rate, and oxygen saturation. Depending on the clinical presentation and setting, an electrocardiogram, a chest x-ray or computed tomography scan of the thorax, blood gas assessment, and blood sampling for, e.g., C-reactive protein (CRP), blood cells, or fibrin d-dimer may be indicated.

When AECOPD is diagnosed, the principal treatment is inhaled short-acting bronchodilators (beta-2-agonists and muscarinic antagonists). Five days' treatment with OCS is indicated in moderate and severe AECOPDs. Those with sputum purulence and increased sputum or dyspnoea should be given five days' treatment with antibiotics. Oxygen is administered if there is

hypoxaemia. In the case of hypercapnia or respiratory failure despite such measures, non-invasive or invasive ventilatory support is indicated. After an AECOPD, patients should be followed up thoroughly, and all measures should be taken to prevent further events.

1.11 Mortality in COPD

Globally, COPD is estimated to cause approximately 3 million deaths annually and is one of the leading causes of life-years lost.¹⁷ Patients with COPD suffer about three times higher risk of all-cause mortality than the general population.¹¹¹ In Sweden, life expectancy is 8.3 years shorter in patients with COPD than in the general population.¹¹¹ Main causes of death are essentially the same as in the general population – heart disease and cancer – but the risk of respiratory death is substantially increased, as is the risk of lung cancer.¹¹¹ However, causes of death vary with disease severity, i.e., the lower the FEV₁, the greater the proportion of patients suffering respiratory death.⁷⁵

Comorbidities increasing the risk of COPD mortality are mentioned above. Numerous other risk factors have been described, including high age, low socioeconomic status, impaired FEV₁, dyspnoea, decreased exercise capacity, cachexia, and failure to quit smoking.^{9,59,112-115} Also, biomarkers of systemic inflammation have been associated with increased mortality.^{108,116} Among the most robust predictors, however, are hospitalisations and AECOPDs.^{96,97,117}

There is evidence that specific treatments for COPD can modify the risk of death. Smoking cessation and early pulmonary rehabilitation after an AECOPD are cheap and cost-efficient interventions with beneficial effects on survival.^{9,118} A more expensive approach, with survival benefits in select patients with severe emphysema, is lung volume reduction surgery.¹¹⁹ Patients with very severe COPD and hypercapnia may benefit from long-term non-invasive ventilation at home.¹²⁰ Home oxygen therapy for severe COPD with respiratory failure confers decreased mortality,^{121,122} and was for a long time the only pharmacological treatment considered effective in reducing COPD deaths.

As for LAMAs, there was some hope that mortality would be reduced when the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) randomised controlled trial (RCT) reported a positive signal.¹²³ The Cochrane Library, on the other hand, did not find a significant effect on mortality when reviewing 22 RCTs comparing tiotropium to placebo,¹²⁴ and LAMAs are today considered neutral concerning mortality.

Although observational studies have suggested that ICS may improve COPD survival, controlled trials have failed to prove such an effect for several years.^{125,126} In the last half of a decade, trials evaluating the impact of adding ICS to LABA+LAMA have brought new evidence suggesting that ICS decrease mortality among COPD patients with a high symptom burden and a

significant AECOPD history.¹²⁷⁻¹²⁹ Interestingly, there is also evidence that the beneficial effect of ICS is greater for people with higher B-Eos,¹²⁸ which is one of the reasons B-Eos is now recommended as a predictive biomarker to find the COPD patients most likely to benefit from ICS.¹² These results have been questioned, and the benefit of adding ICS to LABA/LAMA could not be extended to a general, non-trial COPD population in a large, real-world study.¹³⁰

Few trials have studied the treatment of comorbidities specifically in COPD. However, there are many observational data suggesting beneficial effects on survival of various pharmacological treatments not approved for COPD, e.g., statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEis), angiotensin-II receptor blockers (ARBs) antidepressants, and acetylsalicylic acid (ASA).¹³¹⁻¹³⁷ Several of these studies have been criticised,¹³⁸⁻¹⁴⁰ and in most cases RCT data is lacking or insufficient. Two large RCTs on non-COPD treatments have been performed: statins did not reduce mortality (or the AECOPD frequency)¹⁴¹ and the beta-blocker metoprolol did not reduce mortality¹⁴² in COPD patients with no approved indication for the study treatment.

1.12 Prognostic tools

Table 4. Multidimensional tools developed to predict mortality in COPD.¹⁴³ The list is not exhaustive.

Tool	Components
ADO	Age, dyspnoea (mMRC), airflow obstruction (FEV ₁)
B-AE-D	BMI, AECOPD, dyspnoea (mMRC)
BODE	BMI, airflow obstruction (FEV ₁), dyspnoea (mMRC), exercise capacity (6MWT)
e-BODE	AECOPD, BMI, airflow obstruction (FEV ₁), dyspnoea (mMRC), exercise capacity (6MWT)
BODEx	BMI, airflow obstruction (FEV ₁), dyspnoea (mMRC), AECOPD
DOSE	Dyspnoea (mMRC), airflow obstruction (FEV ₁), current smoking, AECOPD
SAFE	Saint George's Respiratory Questionnaire score, airflow obstruction (FEV ₁), exercise capacity (6MWT)

Abbreviations: COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council dyspnoea scale; FEV₁, forced expiratory volume in one second; BMI, body mass index; AECOPD, acute exacerbation of COPD; 6MWT, six-minute walking test.

Several multidimensional tools to predict COPD mortality have been created, such as the ADO,^{144,145} the BODE (and modified versions e-BODE and BODEx),^{144,146,147} the DOSE indices,¹⁴⁸ and others (Table 4).¹⁴³ In this setting, 'multidimensional' refers to integrating different measures of COPD morbidity (and age) known to be prognostic. The BODE index is the most studied,

and hence is recommended by GOLD,¹³ but the ADO index performs best.¹⁴³ However, none of these indices acknowledge the mortality risk associated with comorbidities.

An algorithm for mortality prediction was developed by Burgel *et al.* in 2017 (page 43).¹⁴⁹ It includes specified comorbidities (HF, coronary artery disease, hypertension, and diabetes) and four other factors (mMRC score, FEV₁, age, and body mass index [BMI]) that are significant predictors of mortality.^{59,113,114,150} The algorithm allocates COPD patients to five groups, or phenotypes, with different mortality risks. In two subsequent studies, the algorithm was validated for mortality prediction in other populations and over extended follow-up periods.^{151,152}

There have been several attempts to develop prognostic tools for AECOPDs,^{153,154} but none is currently recommended by GOLD (except taking AECOPD history). However, the ACCEPT (Acute COPD Exacerbation Prediction Tool) is a promising online tool.¹⁵⁵ It incorporates 13 items and uses a mathematical model to predict an individual risk.

1.13 Phenotypes, endotypes, and treatable traits

COPD is heterogeneous in the sense that there is no single mechanism leading to the disease, no single clinical presentation, and no single treatment fitting all patients. Instead, COPD can be considered an umbrella term covering several entities with different genetic and pathophysiological backgrounds and different presentations.¹⁵⁶ Clinically, this may be described as different *phenotypes*. While the classic definition of a phenotype is broader, the following definition has been proposed for COPD:

[...] a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death).¹⁵⁷

In other words, the definition aims not only to categorise COPD patients based on clinical presentation but also to do it in a way that helps patients and clinicians manage the disease. At least since the middle of the 20th century, chronic bronchitis and emphysema phenotypes have been recognised.² Over the years, several other phenotypes have been proposed, with the frequent exacerbator phenotype being one of the most established.¹⁰⁵ Some phenotypes are clear and distinct and relatively easy to define. However, most patients will not be defined by a single phenotype but rather fit into several or partly fit into some. Moreover, a phenotype can have different causes in different patients, i.e., more than one pathophysiological mechanism can lead to the same clinical

presentation. Therefore, the concept of phenotypes can be hard to apply in both clinical situations and research.

An attempt to better understand the heterogeneity of COPD phenotypes is by linking them to *endotypes* (Figure 5).¹⁵⁸ This concept refers to ‘[...] a subtype of a (clinical) condition defined by a distinct pathophysiological mechanism’.¹⁵⁹ An endotype can result in several phenotypes, and a phenotype can result from several endotypes. Multiple biomarkers and clinical phenotype assessments are usually necessary to identify endotypes. In COPD, the most well-described endotype is alpha-1 antitrypsin deficiency.¹⁶⁰ Other proposed endotypes include neutrophilic COPD¹⁶¹ and eosinophilic COPD,¹⁶² although controversy exists.¹⁶⁰ While this may be more useful in the future, the clinical benefits of referring patients to endotypes are currently limited, as our understanding of the pathophysiology leading to COPD is incomplete, and several endotypes may be present in the same patient. Nonetheless, characterising the precise biological mechanisms leading to disease opens for future individualised treatment.

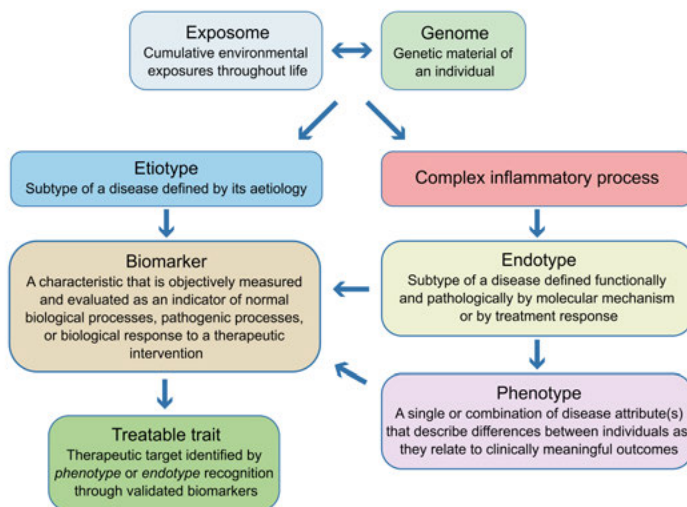


Figure 5. Schematic illustration of key concepts in the current understanding of airway diseases and how they relate to each other. Adapted from Agustí A, Bafadhel M, Beasley R, *et al.* Precision medicine in airway diseases: moving to clinical practice. *Eur Respir J.* Oct 2017;50(4):1701655.

Recognising the complexity of COPD (and asthma) and the difficulties sorting patients into ‘boxes’ of phenotypes or endotypes, the concept of *treatable traits* has been developed (Figure 5).¹⁶³ In this approach, each patient with suspected airway disease is thoroughly and systematically assessed for specified phenotypic or endotypic expressions for which treatment is available.¹⁶⁴ Importantly, extrapulmonary traits and behavioural/lifestyle risk factors are

assessed, as well as pulmonary traits. Extrapulmonary traits refer mainly to comorbidities that influence the course of the disease.

The latest contribution to categorising COPD patients into clinically meaningful groups is the etiotypes discussed above.^{13,14} In contrast to the endotypes, which aim to clarify the mechanisms leading to COPD, the etiotypes focus solely on the aetiology of COPD.

Future research will show which of these concepts, if any, prevail.

1.14 Biomarkers

Several definitions of the term *biomarker* exist, although most are rather similar. The United States Food and Drug Administration (FDA) and National Institute of Health initiative BEST (Biomarkers, EndpointS, and other Tools) define it as follows:

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics. A biomarker is not a measure of how an individual feels, functions, or survives.¹⁶⁵

According to BEST, there are seven categories of biomarkers, of which *prognostic biomarkers* are relevant for this thesis. Prognostic biomarkers are used to predict clinical events, such as disease progression or exacerbations, in patients with a specific diagnosis. They should not be confused with *predictive biomarkers*, used to identify those patients most likely to have a particular effect of a treatment or intervention. The same biomarker can be included in several categories, depending on the setting.

A biomarker for long-term predictions should be reasonably stable, i.e., generate the same prediction or recommendation when analysis is repeated, provided that the condition is otherwise stable. Therefore, it is essential to have knowledge of the longitudinal properties of biomarkers, e.g. their reliability.¹⁶⁶

1.14.1 Blood-based inflammatory biomarkers in COPD

Many potential biomarkers have been investigated in COPD research for a large number of purposes, e.g., to understand pathobiological processes, to improve the diagnostics of COPD or AECOPD, and to predict various outcomes.¹⁶⁷ The insight discussed above that COPD is associated with increased systemic inflammation sparked considerable interest in blood-based biomarkers.^{167,168} As for prognostic biomarkers, several candidate biomarkers have been analysed in different settings as regards prediction of various

outcomes.^{167,169} In the following, the biomarkers relevant for this thesis will be reviewed.

1.14.2 CRP

CRP is an acute-phase protein mainly produced by hepatocytes.¹⁷⁰ The acute-phase response is highly non-specific and can be induced by almost any inflammation, infection, tissue damage, or neoplasia.¹⁷⁰ This response involves upregulation and release of many proteins into the blood circulation in response to signalling substances, e.g., cytokines. The proteins have various functions in the body's defence systems. CRP binds to exposed autologous and/or exogenous, e.g., microbial, structures, where it activates the classical complement pathway and/or acts as a proinflammatory mediator.¹⁷⁰ It is one of the fastest acute-phase proteins and highly sensitive to cytokine stimulation.

Clinically, CRP is widely used in many settings, e.g., to help diagnose infections, to follow up on treatment effects, and to monitor chronic inflammatory diseases. It is analysed from blood samples, and the analysis is inexpensive and available at almost every healthcare facility, at least in high-income countries. However, as it is highly non-specific, i.e., can be induced by a wide range of pathologies, CRP must always be combined with other information, such as patient history or other biomarkers.¹⁷⁰ On its own, it is of limited value.

CRP is higher in people with COPD than in healthy controls,^{42,168} and elevated levels are associated with increased risk of cardiovascular diseases and COPD mortality.^{108,171,172} Moreover, CRP has been studied during AECOPDs as a tool to diagnose AECOPD¹⁷³ and determine the need for antibiotics.¹⁷⁴ There are also several reports associating elevated CRP during stable COPD with increased risk of future AECOPDs, although that association disappears when adjusting for confounders^{99,169,175} or applies only to severe AECOPDs.¹⁷⁶⁻¹⁷⁸ Two studies have reported that CRP in combination with other biomarkers are prognostic of AECOPDs,^{168,179} Agustí *et al.* used CRP, B-Leu, interleukin-6, and fibrinogen combined,¹⁶⁸ whereas Thomsen *et al.* used CRP, B-Leu, and fibrinogen combined¹⁷⁹ to predict AECOPDs. CRP measures are currently not recommended for clinical use in relation to COPD.

1.14.3 Fibrinogen

Like CRP, fibrinogen is an acute-phase protein mainly produced in hepatocytes and is induced non-specifically as a response to various insults to body tissues.¹⁸⁰ It is a significant component of plasma, and increased levels are a major cause of the elevated erythrocyte sedimentation rate seen in various states of inflammation. Moreover, fibrinogen is a coagulation factor and plays a vital role in both primary and secondary haemostasis.¹⁸⁰

Fibrinogen links platelets by binding to the glycoprotein receptor GP IIb/IIIa, expressed on activated platelets, i.e., fibrinogen promotes platelet

adhesion and aggregation (primary haemostasis).¹⁸⁰ Thrombin cleaves fibrinogen into fibrin and fibrinopeptides. Fibrin monomers are then crosslinked in a process catalysed by activated factor XIII into polymers (secondary haemostasis) that stabilise the platelet clots formed during primary haemostasis.¹⁸⁰ Accordingly, low levels of fibrinogen are associated with an increased risk of bleeding, and high levels with an increased risk of venous and arterial thrombosis, e.g., venous thromboembolism, MI, and stroke.

The clinical use of fibrinogen is not as widespread as that of CRP, and analysis is more expensive. Nonetheless, it is used to assess, e.g., suspected coagulopathies or disseminated intravascular coagulation, and sometimes to monitor fibrinolytic therapy.

In patients with COPD, fibrinogen levels are higher than in healthy controls.^{42,168} Moreover, elevated fibrinogen is associated with increased mortality risk,^{108,178,181} and several studies have found it to be prognostic of moderate/severe AECOPDs¹⁸¹⁻¹⁸⁴ or severe AECOPDs.^{178,185} However, some authors have reported conflicting results.^{99,169} As noted in the section on CRP above, fibrinogen, in combination with other biomarkers, predicts AECOPDs.^{168,179,186} Fibrinogen is approved by the FDA for use as a prognostic biomarker in interventional clinical trials regarding COPD to enrich the study populations with participants with high risk of AECOPDs and/or mortality.¹⁸⁷ However, it is currently not recommended for clinical use.

1.14.4 Platelets

Platelets (thrombocytes) are derived from their progenitor cells (megakaryocytes) in the bone marrow and the lungs.¹⁸⁸ They are best known for their role in primary haemostasis, but they are, in fact, also involved in inflammatory processes and participate in the immune response to various pathogens.¹⁸⁹ Smoking makes platelets more prone to aggregation, and data suggest that platelets are involved in the pathogenesis of COPD.¹⁸⁸ Moreover, mean levels of blood platelets (B-Plt) are higher in COPD than in controls.¹⁹⁰ There is also evidence that B-Plt activation is higher in stable COPD than in healthy controls and even higher in AECOPDs.¹⁹¹ An RCT found that the thrombocyte-inhibiting effect of ASA was lower than anticipated in patients with COPD, which was interpreted as proof of a pro-thrombotic state.¹⁹² These data suggest that B-Plt reflect systemic inflammation in COPD. One study has reported an association between B-Plt and future AECOPDs, but that association was not retained in a multivariable model.⁹⁹

1.14.5 Leukocytes

Leukocytes (white blood cells) are immune cells derived from the bone marrow. They are found circulating in the blood and infiltrating tissues. There are several types of leukocytes, with different roles in the immune system. The

leukocyte types of principal interest for this thesis – neutrophils, lymphocytes, eosinophils, and monocytes – will be reviewed briefly below, but there are also several other leukocyte types that are beyond the scope of this presentation. Total blood leukocytes (B-Leu) are a non-specific measure of the total amount of all leukocyte types in blood, and are frequently used in routine healthcare as a biomarker of, e.g., infectious, inflammatory, and haematological conditions.

In COPD, mean B-Leu are higher than in healthy controls,^{42,168} and the levels seem to increase with the severity of airflow obstruction.¹⁷² Higher B-Leu are associated with an increased mortality risk in COPD.¹⁰⁸ Regarding the prediction of AECOPDs, data are conflicting. Association with an increased AECOPD risk has been reported,^{99,185} although other studies found no association when confounders were considered.^{175,193} As noted in the section on CRP above, B-Leu, in combination with other biomarkers, predict AECOPDs.^{168,179}

1.14.6 Neutrophils

Neutrophils are central to the pathogenesis of COPD, regardless of clinical features and disease severity, and also play an important role in AECOPDs.^{31,194} Neutrophils release proteases, reactive oxygen species, and neutrophil extracellular traps, and contribute to pro-inflammatory signalling.³¹ Their role in the development of emphysema and mucus hypersecretion is well-established.¹⁹⁴ Reports suggest that neutrophil dysfunction may be a critical pathobiological mechanism and that there may be interactions between neutrophilic inflammation and the airway microbiome.¹⁹⁴

Blood neutrophils (B-Neu) do not necessarily reflect pulmonary neutrophilic inflammation.¹⁹⁵ Nonetheless, observational data suggest that patients admitted for AECOPD have worse outcomes if B-Neu are elevated.¹⁹⁶ Moreover, *post hoc* analyses of RCT data indicate that higher B-Neu increase the risk of pneumonia,¹⁹⁷ and real-world data have shown that higher B-Neu predict AECOPD frequency and long-term mortality.¹⁹⁸

1.14.7 Lymphocytes

Various types of lymphocytes contribute to the inflammatory processes in the COPD-afflicted lung by releasing cytotoxic substances and pro-inflammatory mediators.³³ Blood lymphocytes (B-Lym) have an altered subtype distribution in COPD compared with healthy controls.¹⁹⁹ Moreover, levels of B-Lym are lower, and the longitudinal B-Lym decrease is greater in people with COPD than in healthy smokers.²⁰⁰ COPD patients with declining B-Lym have a higher incidence of cancer and increased mortality risk,²⁰⁰ and low B-Lym are associated with increased mortality risk, faster FEV₁ decline, lower quality of life, and worse exercise capacity.²⁰⁰⁻²⁰² Low B-Lym are associated with increased mortality also in the general population.²⁰³

1.14.8 Eosinophils

Although neutrophils are the most abundant immune cells in the COPD lung, approximately one-third of COPD patients exhibit a concurrent eosinophilic inflammation, also referred to as *type 2 inflammation*, which is frequently associated with asthma.²⁰⁴ The role of eosinophils in COPD remains to be elucidated. Still, there are indications that they may contribute to pathogenesis through direct cytotoxic effects, as well as pro-inflammatory signalling leading to increased mucus secretion and airway remodelling.³¹ A significant proportion of AECOPDs are characterised by eosinophilic inflammation.¹⁰²

Compared with healthy controls, patients with COPD have higher levels of eosinophils not only in sputum but also in blood (B-Eos) similar to the levels seen in asthmatics.^{205,206} B-Eos correlate with eosinophilic inflammation in the lung.^{195,207,208} The results of observational studies on the ability of B-Eos to predict AECOPDs are conflicting, where some have found levels to be prognostic²⁰⁹⁻²¹⁵ whereas others found no such association.²¹⁶⁻²²⁴ Some authors have noted increased mortality in COPD patients with high B-Eos,²²⁵ but others report the opposite^{196,217,223,226,227} or no difference.²¹⁸ There may be several explanations for these differences across studies, including different B-Eos cut-offs used and different methodological approaches to factors known to influence B-Eos in respiratory disease, such as sex,²²⁸ BMI,²²⁹ comorbid asthma,^{228,230} smoking status,²³¹ ICS use,²³² and OCS use.²³³ Moreover, within-day and between-day variability of B-Eos may affect study results; one study found that 50% of the participants changed strata when repeatedly measured over a day.²³⁴ On the other hand, studies show fair longitudinal stability of B-Eos measurements in COPD.^{217,223,235-239}

It should be noted that ‘high’ in the context of B-Eos and COPD often refers to values above $0.15\text{--}0.3 \times 10^9$ cells/L, which is usually well within normal. All Swedish laboratories are recommended to use $< 0.5 \times 10^9$ cells/L as a reference range.²⁴⁰ As mentioned above, B-Eos is recommended by GOLD as a predictive biomarker of response to ICS therapy,¹² as the effect of ICS added to bronchodilators is better with regard to, e.g., AECOPD reduction and mortality in COPD patients with higher B-Eos.^{128,129,241,242}

1.14.9 Monocytes

Monocytes are pro-inflammatory leukocytes found in blood. They migrate to sites of pathology where they have several functions, such as pro-inflammatory signalling, phagocytosis, antigen presentation, and complement activation.²⁴³ There are different subsets of monocytes with partly different but overlapping functions. Depending on the microenvironment, monocytes may differentiate into dendritic cells or macrophages.²⁴³ The latter are believed to be of significance in COPD.²⁴⁴ In severe COPD, blood monocytes (B-Mon) are elevated compared with in healthy controls, and the monocytes have

properties that make them prone to migration into the lungs, where they may differentiate into macrophages that contribute to the destructive, inflammatory process.^{243,244} One study has found that B-Mon measured during stable-phase COPD are independently associated with future AECOPDs.²⁴⁵

1.14.10 Blood cell indices: NLR, PLR, SII, SIRI, and AISI

Recognising the various functions of blood cells and their varying associations with disease mechanisms and outcomes, several attempts have been made to enhance their performance as biomarkers by combining them into indices. Such indices have been studied in many disorders and many different settings. Part of the scientific attractiveness of this approach lies in the wide availability of the analyses, their low cost, and the fact that the blood cells are often analysed anyway, as part of routine care.

One of the most studied indices is the neutrophil-to-lymphocyte ratio (NLR), obtained by dividing B-Neu by B-Lym. In recent decades, this biomarker has gained increasing interest as a predictor of important outcomes within oncology, cardiology, neurology, and numerous other fields, as well as in the general population.²⁴⁶ Higher values are generally associated with worse outcomes.

A cohort study suggests that NLR is a risk factor for lung function decline and future diagnosis of COPD.²⁴⁷ In COPD, NLR is higher than in healthy controls and further increased in AECOPDs.²⁴⁸⁻²⁵⁰ At admission, NLR can predict a diagnosis of AECOPD,²⁴⁸ and NLR obtained during AECOPD or hospitalisation can predict outcomes such as the need for readmission and mortality.^{251,252} There are also data suggesting that NLR obtained during a stable phase of COPD can predict AECOPDs and mortality.^{116,253-257} However, meta-analyses and systematic reviews conclude that data are scarce and more studies are needed.^{248,249}

In analogy to NLR, the platelet-to-lymphocyte ratio (PLR) is obtained by dividing B-Plt by B-Lym. PLR is higher in stable COPD than in healthy controls, and even higher in AECOPD.¹⁹⁰ PLR obtained at admission predicts mortality in AECOPD,²⁵² and one study has suggested that PLR measured during stable-phase COPD can predict future AECOPDs.²⁵⁸

The systemic immune-inflammation index (SII), the systemic inflammation response index (SIRI), and the aggregate index of systemic inflammation (AISII) are novel biomarkers. They are calculated as follows: $SII = B\text{-Neu} \times B\text{-Plt} / B\text{-Lym}$; $SIRI = B\text{-Neu} \times B\text{-Mon} / B\text{-Lym}$; $AISII = B\text{-Neu} \times B\text{-Plt} \times B\text{-Mon} / B\text{-Lym}$. Although these indices have been studied in other diseases, only a few publications concerning COPD exist.^{50,258,259} SII has been associated with increased mortality risk in COPD⁵⁰ and AISII with increased mortality in COPD patients hospitalised due to covid-19.²⁵⁹ The same report indicating an association between PLR and future AECOPDs also reported that SII and SIRI were associated with AECOPDs.²⁵⁸

2 Aims

This thesis aimed to find prognostic risk factors for COPD mortality and exacerbations, focusing on comorbidities and inflammatory biomarkers.

The specific aims of the included papers were:

- I. To examine associations between comorbidities and pharmacological treatment on the one hand and mortality on the other, in a large real-world cohort of primary care COPD patients.
- II. To test the hypothesis that the biomarkers neutrophil-to-lymphocyte ratio and blood eosinophils can predict future COPD exacerbations and determine the longitudinal stability and reliability of the biomarkers.
- III. To analyse whether CRP, fibrinogen, leukocytes, or four blood cell indices can predict future exacerbations of COPD.
- IV. To investigate whether previously described clinical COPD phenotypes can predict future exacerbations of COPD, validate the phenotypes' ability to predict mortality, and cross-sectionally investigate associations between the phenotypes and baseline blood-based biomarkers of inflammation.

3 Methods

3.1 Populations, study design, and data sources

PATHOS (Paper I)

PATHOS was a population-based, retrospective, partly register-based cohort study. Medical record data from 76 Swedish primary care healthcare centres were linked to data from mandatory Swedish national registers (National Patient Register for data on inpatient care and outpatient secondary care, Cause of Death Register, Prescribed Drugs Register) and demographic/socioeconomic data from the governmental authority Statistics Sweden. Patients with a new diagnosis of COPD (International Classification of Diseases, 10th revision [ICD-10] diagnosis J44) between 1 January 1999 and 31 December 2009 were included in this analysis (n = 17,745). The only exclusion criterion was a COPD diagnosis only in the Cause of Death Register. The index date was the date of the first COPD diagnosis, and patients were followed until 31 December 2009, emigration, or death.

TIE (Papers II–IV)

In the Tools Identifying Exacerbations in COPD (TIE) cohort study, 572 participants with a COPD diagnosis were recruited from primary and secondary care in the three Swedish regions of Dalarna, Gävleborg, and Uppsala between September 2014 and September 2016 (Figure 6). At the baseline visit and two subsequent yearly visits (all in a stable phase of COPD, i.e., at least four weeks after the latest AECOPD), spirometry and phlebotomy were performed, and participants answered questionnaires. In addition, medical records were reviewed for AECOPDs from one year before baseline until three years after baseline or death.

In Paper II, only participants with complete data on the main study variables at one or more visits were included for the main analysis of the relation between blood cells and AECOPD (n = 466) and only subjects with complete data on blood cells at all three visits were included in the secondary analysis of longitudinal stability (n = 386). Follow-up lasted until the last visit (i.e., for two years).

In Paper III, all TIE participants were included in the study population except one participant retrospectively excluded due to severe comorbidity, resulting in a study population of n = 571. The follow-up lasted from the

baseline visit until the end of the medical record review (i.e., for three years) or until death.

In Paper IV, participants with complete data on the baseline variables needed for allocation to a clinical COPD phenotype in accordance with Burgel *et al.*¹⁴⁹ were included. One subject was excluded due to retrospectively found severe comorbidity. The study population consisted of n = 566 participants. The follow-up time was identical to that in Paper III.

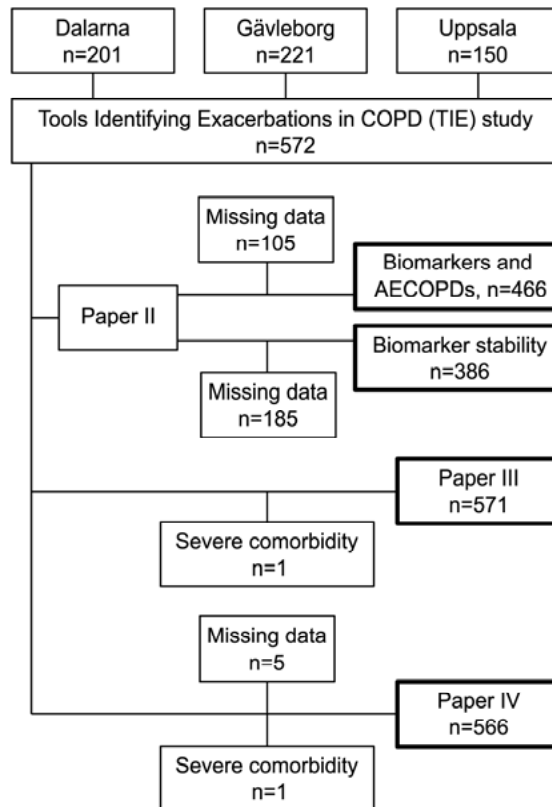


Figure 6. Schematic diagram describing the differences between the study populations in Papers II-IV, all based on the TIE study. For full details, see the individual Papers. Abbreviations: COPD, chronic obstructive pulmonary disease; TIE, Tools Identifying Exacerbations in COPD study; AECOPD, acute exacerbation of COPD.

3.2 Ethics

The PATHOS study and the TIE study had ethical approvals from the Regional Ethics Committee in Uppsala, Sweden (Dnr 2010/040 and Dnr 2013/358, respectively). No informed consent was obtained in PATHOS, but

all data were anonymised. In TIE, all participants provided written informed consent, and data were pseudonymised.

3.3 Definitions of COPD

In PATHOS, COPD was defined as the occurrence of the ICD-10 diagnosis code J44 in medical records. The basis of the diagnosis was not investigated further, and no verification by spirometry was done.

In TIE, a previous diagnosis of COPD was an inclusion criterion. Furthermore, chronic airflow obstruction confirmed through spirometry was required. It was defined as a ratio of post-bronchodilator FEV₁ to the highest of FVC and SVC < 0.7.

3.4 Variables used in the papers

3.4.1 Outcomes

Paper I

The outcome was all-cause mortality, obtained from the Cause of Death Register.

Paper II

The outcome was self-reported AECOPDs during a period of 12 months, obtained from questionnaires distributed at each study visit.

Paper III

The outcome was AECOPD frequency during the three-year follow-up. The number of AECOPDs was identified by a review of medical records and divided by the duration of the observation to produce a rate (number per year).

Paper IV

The outcomes were time to first AECOPD and time to all-cause death, both identified by review of medical records. Moreover, blood-based biomarkers of inflammation, including CRP, fibrinogen, blood cells, and several indices derived from the blood cells, were outcomes.

3.4.2 Exacerbations of COPD

In PATHOS, AECOPDs were defined as one or more of the following events: COPD-related hospitalisation (ICD-10 code J44 as primary diagnosis or J44.0/J44.1 as secondary diagnosis), emergency visit (ICD-10 codes

J44.0/J44.1), or collection of prescribed short-term oral corticosteroids (OCS) or antibiotics used for AECOPD.

In TIE, AECOPDs were assessed in two ways. First, participants answered questionnaires covering the preceding 12 months where an AECOPD was defined as an acute healthcare visit and/or short-term use of oral corticosteroids and/or antibiotics due to worsening of COPD. This definition was used in Paper II. Second, medical records were reviewed, where the AECOPD definition was ‘an unscheduled or scheduled health care visit with increased respiratory symptoms leading to inhalation of bronchodilators (at the health care facility), and/or treatment with OCS, and/or treatment with antibiotics, and/or referral to the emergency department, and/or hospitalisation due to COPD’. The date of the first AECOPD after baseline was recorded. The latter definition was used in Papers III and IV.

Events occurring within 14 days were regarded as one AECOPD only in both PATHOS and TIE.

3.4.3 Anthropometric, demographic, and socioeconomic factors

In PATHOS, demographic and socioeconomic data provided by Statistics Sweden included age, yearly income, marital status, and educational level. There were no anthropometric data.

In TIE, age, height, and weight were collected at study visits, and BMI was calculated as the ratio of weight (kg) to height (m) squared.

3.4.4 Spirometry

In PATHOS, lung function data were available only for a small minority of the population; therefore, these data were not included in Paper I.

In TIE, all participants underwent spirometry 15 minutes after inhalation of 400 µg salbutamol. The spirometry was performed in accordance with international standards and by trained staff.²⁶⁰ FEV₁, SVC, and FVC (litres) were obtained; the former was also expressed as per cent predicted based on Swedish reference values.^{261,262}

3.4.5 Symptoms

In PATHOS, there were no data on symptoms.

In TIE, symptoms were assessed with the mMRC⁶¹ and the CAT.⁶⁰ An mMRC score ≥ 2 and/or a CAT score ≥ 10 were considered a high burden of symptoms.¹² The CAT score, although strictly containing only categorical data, was treated as odds ratio data for analytical purposes.

3.4.6 Comorbidities

PATHOS

Comorbidities were identified based on ICD-10 codes: asthma (only considered before baseline), pneumonia (only considered within two years before baseline), diabetes, depression, hypertension, acute MI, IHD, HF, stroke, osteoporosis, and fractures. The CCI as adapted by Quan *et al.* was calculated based on data from the two years preceding baseline.^{77,263}

TIE

In Papers II–IV, comorbidities were self-reported at baseline visits in a binary fashion (the patient answering yes or no to whether they presently had or previously had had the condition of interest). Conditions assessed were asthma, chronic bronchitis, coronary heart disease (CHD, i.e., MI and/or angina pectoris), diabetes, HF, hypertension, and depression or anxiety.

3.4.7 Pharmacological treatment

PATHOS

Using data from the Prescribed Drugs Register, drug usage from two years before baseline until the end of follow-up was analysed and updated every year. To examine any exposure dependency, drug usage was assessed both as any use of and as relative exposure to the drug class of interest. Relative exposure was calculated based on the prescribed dose, prescription frequency, pack size and dispensed items, generating a cumulative number of defined daily doses, then divided by the total number of days of exposure to the drug during the preceding three years. The following drug classes were included: ICS, LABAs, fixed combination of ICS and any LABA, LAMAs (tiotropium bromide, as it was the only LAMA available in Sweden during the study period), NAC, OCS, bisphosphonates, statins, ASA, ACEis, beta-blockers, ARBs, diuretics, and selective serotonin reuptake inhibitors (SSRIs).

TIE

Baseline pharmacological treatment was assessed through questionnaires. Current use was defined as any use during the six months preceding the study visit. The following drug classes were considered: ICS, LABAs, LAMAs, and long-term oxygen.

3.4.8 Blood-based biomarkers of inflammation

In PATHOS, no blood-based biomarkers were available.

In TIE, biomarkers of inflammation were analysed in blood samples drawn at each study visit. All analyses were performed at the local hospital laboratory at the three study sites, using routine clinical equipment. Blood cells were

analysed with Cell-Dyn 4000 and Sapphire (Abbott Laboratories, IL, USA) and Sysmex XN-10 and XN-20 (Sysmex Corporation, Japan). CRP was analysed with Architect ci8200 and c16000 (Abbott Laboratories, IL, USA), Cobas 6000 (Roche Group, Switzerland), and ADVIA 1800 (Siemens Healthcare GmbH, Germany). Plasma fibrinogen was analysed with Architect c16000, Cobas 6000, STA R Max (Stago Group, France), and Sysmex CS2100i (Sysmex Corporation, Japan).

The following blood cells were counted: B-Plt, B-Leu, B-Neu, B-Eos, B-Lym, B-Mon, and basophils (B-Bas). For dichotomised analyses, the upper reference value of the laboratory at the Uppsala site was used, except for B-Eos, B-Bas and B-Lym. B-Eos was dichotomised using the threshold value of $\geq 0.3 \times 10^9$ cells/L proposed by GOLD.¹² B-Bas was dichotomised after the upper quartile of the TIE population ($\geq 0.09 \times 10^9$ cells/L) as the laboratory's upper reference value ($> 0.1 \times 10^9$ cells/L) did not yield a large enough group with high levels ($n = 7$). B-Lym was dichotomised based on the threshold value of $\geq 1.8 \times 10^9$ cells/L suggested by Semenzato *et al.*²⁰⁰

Haematological indices were calculated (NLR = B-Neu / B-Lym; PLR = B-Plt / B-Lym; SII = B-Plt x B-Neu / B-Lym; SIRI = B-Mon x B-Neu / B-Lym; and AISI = B-Plt x B-Mon x B-Neu / B-Lym). As there are no established threshold values, the upper quartile of the TIE population was used to define high levels: NLR ≥ 3.1 (in Paper II, the upper quartile of the studied subpopulation [$n = 466$] was used: NLR ≥ 3.0), SII ≥ 856 , SIRI ≥ 2.024 , AISI ≥ 533 , and PLR ≥ 169.1 .

CRP and fibrinogen were analysed as both continuous and dichotomised variables, using the Uppsala laboratory's upper reference range as the threshold for CRP (≥ 5 mg/L) and that proposed by Mannino *et al.*¹⁸¹ for fibrinogen (≥ 3.5 g/L).

3.4.9 Clinical COPD phenotypes

In Paper IV, participants were allocated to clinical COPD phenotypes 1–5 using an algorithm previously described by Burgel *et al.*¹⁴⁹ The algorithm contains the following five items: 1) any history of the comorbidities HF, CHD, hypertension, and/or diabetes; 2) mMRC score; 3) FEV₁; 4) age; and 5) BMI (Figure 7). The resulting phenotypes 1–5 are also referred to as follows: 1 (severe comorbid), 2 (mixed respiratory/comorbid), 3 (asymptomatic comorbid/obese), 4 (very severe respiratory), and 5 (mild respiratory).

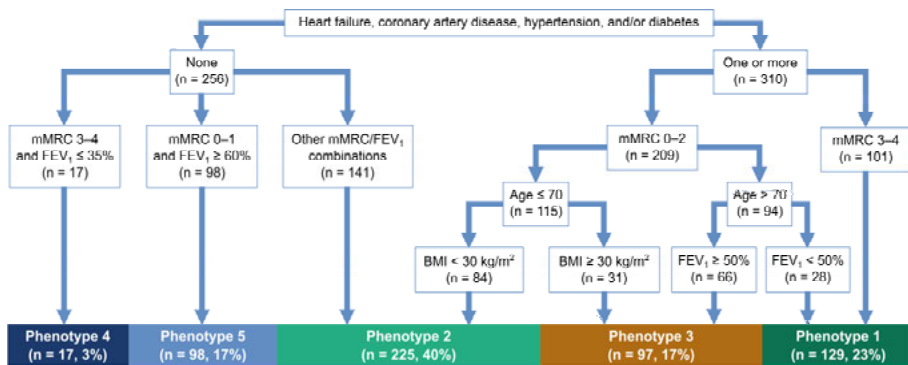


Figure 7. Algorithm for clinical phenotyping, adapted from Burgel *et al.*¹⁴⁹ Abbreviations: mMRC, modified Medical Research Council dyspnoea scale; FEV₁, forced expiratory volume in one second; BMI, body mass index.

3.5 Statistical analyses

Paper I

Hazard ratios (HRs) and adjusted HRs (aHRs) were produced through Cox proportional hazards regression models. First, all variables were analysed separately. Then, all factors with a p-value < 0.2 were entered into a stepwise model, where the lowest Akaike information criterion determined the final model, in which not all variables were included.

Paper II

In this work, data from all three study visits in TIE were used. To accommodate longitudinal data, two-level mixed-effects logistic regression models with future AECOPD within a year as the outcome and NLR and B-Eos, respectively, as predictors were fitted to produce odds ratios (ORs). Adjusted odds ratios (aORs) were produced by including known predictors of AECOPDs into the models: AECOPD history in the preceding 12 months, CAT score, BMI, current smoking, current ICS use, FEV₁, sex, and age. Two-way mixed-effects model single-measurement absolute agreement intraclass correlation coefficients (ICCs)²⁶⁴ were calculated for the reliability of repeated measurements in the same subject.

Paper III

This work based on the TIE cohort used only data from the baseline visit and the medical records review follow-up. The outcome of future AECOPD frequency was divided into four categories corresponding to different frequencies. The following biomarkers of systemic inflammation were studied: CRP, fibrinogen, B-Leu, PLR, SII, SIRI, and AISI. Ordinal logistic regression models were fitted to produce ORs with 95% confidence intervals (CIs) for each

biomarker, analysed separately. Then, aORs were calculated, one biomarker at a time, adjusted for AECOPD history, age, sex, current smoking, BMI, CAT score, FEV₁, and current ICS use.

Paper IV

Like for Paper III, only TIE data from the baseline visit and the medical records review follow-up were used. Time-to-event analyses were performed using Kaplan-Meier estimations (curves compared with the log-rank test) and both unadjusted and adjusted Cox proportional hazards models with the clinical COPD phenotypes as predictors and censoring at the end of the three-year follow-up. The analyses with AECOPD as outcome were adjusted for AECOPD history (used as a stratification variable, as the proportional hazards assumption was violated), age, and current smoking. A competing event (death) occurred before any AECOPD in 26 cases. As the ratio of primary events to competing events was 10:1, using standard Kaplan-Meier estimations and Cox proportional hazards regressions was deemed justified, with participants suffering competing events being censored. The analyses with mortality as outcome were adjusted for AECOPD history, age, sex, and current smoking. Logistic regression models were used to analyse if the phenotypes were associated with any of the following biomarkers of systemic inflammation: B-Plt, B-Leu, B-Neu, B-Eos, B-Lym, B-Mon, B-Bas, NLR, PLR, SII, SIRI, AISI, CRP, and fibrinogen.

4 Results

4.1 Mortality

All-cause mortality was an outcome in Papers I and IV.

Paper I

In the cohort of 17,745 patients with a diagnosis of COPD followed for a total of 64,306 person-years, 5,776 (36.7%) died during the study period. The results of the stepwise multiple Cox regressions are shown in Table 5. Male sex and higher age were associated with an increased mortality risk, whereas higher income and higher education were associated with a decreased risk; marital status did not associate to the risk of death (data not shown in Table 5). Exacerbations and a high CCI score (at baseline) were associated with an increased risk of death, as were the comorbidities HF, MI, IHD, stroke, diabetes, and fractures. In contrast, concomitant asthma and hypertension were associated with a decreased risk of death. The relative exposure to six drug classes reached statistical significance. ICS, LAMAs, and NAC were associated with an increased COPD mortality risk in a dose-dependent manner, whereas beta-blockers, ASA, and SSRIs were associated with a decreased risk.

Table 5 (next page). Mortality risk in COPD by exacerbations, comorbidities, and pharmacological treatment analysed by a stepwise multiple Cox proportional hazards regression model. All variables with a p-value < 0.2 in the simple Cox proportional hazards regression models were entered into the stepwise multiple model. Empty fields indicate variables not included in the final model. Demographic/socioeconomic variables, including sex, age, marital status, yearly income, and education, were also entered, and all but marital status were included in the final model (data not shown). Complete data was available for 16,251 patients.

Notes: a) Per event; b) At baseline only.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; ICS, inhaled corticosteroids; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting beta-2-agonists; ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; SSRIs, selective serotonin reuptake inhibitors.

	aHR	95% CI	p-value
Exacerbations ^a	1.02	(1.01–1.02)	< 0.001
Pneumonias ^b			
Heart failure	1.88	(1.74–2.04)	< 0.001
Myocardial infarction	1.40	(1.24–1.58)	< 0.001
Ischaemic heart disease	1.18	(1.06–1.32)	0.004
Stroke	1.52	(1.40–1.64)	< 0.001
Hypertension	0.90	(0.84–0.96)	0.003
Diabetes	1.13	(1.03–1.23)	0.008
Osteoporosis	1.10	(0.97–1.24)	0.137
Fractures ^a	1.07	(1.04–1.10)	< 0.001
Depression			
Asthma ^b	0.70	(0.64–0.76)	< 0.001
Charlson comorbidity index ^b	1.12	(1.09–1.14)	< 0.001
Any use of the drug class			
ICS			
LAMAs	1.07	(0.98–1.18)	0.138
LABAs	0.87	(0.75–1.00)	0.055
ICS/LABAs, fixed combination			
N-acetylcysteine	0.90	(0.82–0.98)	0.022
Oral steroids	1.16	(1.08–1.25)	< 0.001
Acetylsalicylic acid	1.29	(1.17–1.43)	< 0.001
ACEis	0.82	(0.73–0.93)	0.002
Beta-blockers			
ARBs	0.85	(0.79–0.92)	< 0.001
Diuretics	1.36	(1.26–1.48)	< 0.001
Statins	0.65	(0.60–0.71)	< 0.001
Bisphosphonates	1.21	(1.05–1.40)	0.010
SSRIs	0.82	(0.75–0.90)	< 0.001
Relative exposure to the drug class			
ICS			
LAMAs	1.33	(1.14–1.55)	< 0.001
LABAs	1.25	(0.97–1.61)	0.087
ICS/LABAs, fixed combination			
N-acetylcysteine	1.26	(1.08–1.48)	0.004
Oral steroids			
Acetylsalicylic acid	0.87	(0.77–0.98)	0.022
ACEis			
Beta-blockers	0.86	(0.76–0.97)	0.016
ARBs			
Diuretics			
Statins			
Bisphosphonates			
SSRIs	0.70	(0.56–0.87)	0.001

In a sensitivity analysis, the relative exposure to LAMAs was stratified for concomitant use of ICS (yes or no). Use of LAMAs was dose-dependently associated with a higher risk of mortality both in COPD patients on LAMAs in combination with ICS (aHR 1.24, 95% CI 1.16–1.32, $p < 0.001$) and in those on LAMAs but no ICS (aHR 1.35, 95% CI 1.24–1.47, $p < 0.001$) when compared with patients not using LAMAs.

Paper IV

During the three-year follow-up, 52 of 566 participants (9%) died. The three-year all-cause mortality was numerically highest in phenotype 4 (very severe respiratory) and lowest in phenotype 5 (mild respiratory). Figure 8 shows the Kaplan-Meier estimates of the probability of survival for each phenotype. Cox regressions demonstrated an increased risk of all-cause mortality in phenotypes 1 (severe comorbid), 3 (asymptomatic comorbid/obese), and 4 compared with phenotype 5 (Table 6), even after adjustment for AECOPD history, age, sex, and current smoking. Although the HRs differed numerically, there was no statistical difference between phenotypes 1, 3, and 4, nor between phenotypes 2 (mixed respiratory/comorbid) and 5.

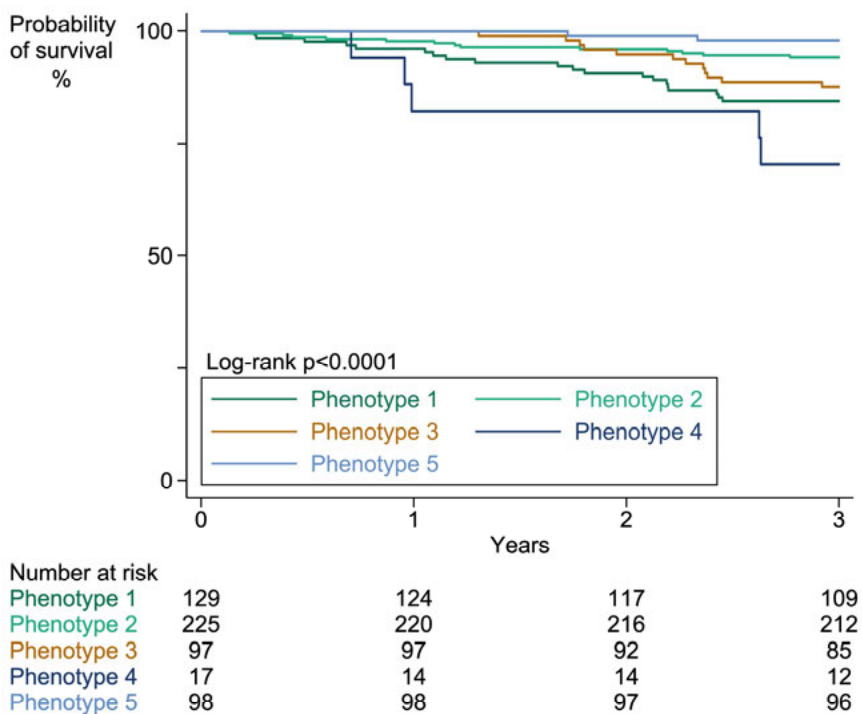


Figure 8. Kaplan-Meier graph showing the cumulative probability of three-year survival, by phenotype, in Paper IV.

Table 6. Relative mortality risk in the TIE study (Paper IV). Cox proportional hazards models of the association between clinical COPD phenotypes and mortality

Phenotype	Unadjusted (n = 566)		Adjusted* (n = 564)	
	HR	95% CI	aHR	95% CI
1, severe comorbid	8.24	1.93–35.3	6.33	1.42–28.3
2, mixed respiratory/comorbid	2.91	0.66–12.9	2.67	0.60–11.9
3, asymptomatic comorbid/obese	6.26	1.40–28.0	5.28	1.15–24.3
4, very severe respiratory	16.7	3.25–86.3	13.4	2.54–71.1
5, mild respiratory	ref		ref	

Notes: * Adjusted for AECOPD history in the year before baseline, age, sex, and current smoking at baseline. Data on smoking were missing for two participants.

Bolded text indicates statistical significance (1 is not included in the 95% CI).

Abbreviations: HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio; AECOPD, acute exacerbation of COPD.

4.2 Acute exacerbations of COPD

AECOPD was an outcome in Papers II–IV. In Paper II, the outcome was binary (any AECOPD during follow-up). In Paper III, the outcome was AECOPD frequency, i.e., the number of AECOPDs divided by follow-up time, grouped into four categories corresponding to different frequencies. In Paper IV, the outcome was time to first AECOPD.

The TIE cohort was used for all three papers, although with different subsets as study populations (see above, section 3.1 Populations, study design, and data sources). In TIE, about 59% were female, 29% were current smokers, and 62% had a CAT score ≥ 10 . The mean \pm standard deviation (SD) FEV₁ was about 57 ± 18 per cent predicted. One-third had experienced ≥ 1 AECOPD in the year before the baseline visit. The percentage with a positive AECOPD history differed slightly between populations due to different AECOPD definitions, but, other than that the percentages were similar across the study populations in Papers II–IV.

Paper II

During the two-year follow-up, 206 of 466 participants (44%) experienced ≥ 1 AECOPD (first year 33%; second year 29%). In the adjusted mixed-effects logistic regression analyses (Table 7), NLR as a continuous variable, but not as a dichotomised variable, was associated with future AECOPDs, whereas B-Eos as a dichotomised variable, but not as a continuous variable, related to future AECOPDs.

Table 7. Mixed-effects multivariable logistic regression models on the association of neutrophil-to-lymphocyte ratio and blood eosinophils with the risk of acute exacerbation of COPD in the subsequent year in Paper II.

	Models with NLR only ^a		Models with B-Eos only ^a		Models combining NLR and B-Eos ^b	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
NLR, continuous	1.20	1.04–1.38	x	x	1.22	1.06–1.40
NLR, ≥ 3.00 vs < 3.00	1.13	0.76–1.68	x	x	1.13	0.76–1.67
B-Eos, continuous ^c	x	x	1.08	0.98–1.20	1.10	0.997–1.22
B-Eos, ≥ 0.3 vs < 0.3 ^d	x	x	1.54	1.06–2.24	1.54	1.06–2.24

Notes: x indicates predictor not analysed. Models adjusted for ≥ 1 AECOPD in the preceding year, CAT score, BMI, current smoking, current ICS use, FEV₁, sex, and age.

a) Each aOR represents a separate model. b) There are two models, one for the two continuous variables and one for the two dichotomous variables. c) Continuous, per 0.1×10^9 cells/L increase. d) $\times 10^9$ cells/L.

Abbreviations: COPD, chronic obstructive pulmonary disease; NLR, neutrophil-to-lymphocyte ratio; B-Eos, blood eosinophils; aOR, adjusted odds ratio; CI, confidence interval; vs, versus; AECOPD, acute exacerbation of COPD; CAT, COPD Assessment Test; BMI, body mass index; ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in 1 second.

Paper III

During the three-year follow-up, 262 of 571 participants (46%) had at least one AECOPD (range 1–28, median 2). The mean \pm SD AECOPD frequency was 0.6 ± 1.2 AECOPDs/year (range 0–9.4), with significantly higher numbers among participants with a history of AECOPD before baseline. Ten per cent had ≥ 2 AECOPDs/year, i.e., were frequent exacerbators.

Several of the analysed blood-based biomarkers of inflammation were associated with AECOPD frequency in the unadjusted ordinal logistic regression analyses (Table 8). After adjustment for AECOPD history, age, sex, current smoking, BMI, CAT score, FEV₁, and current ICS use, only CRP ≥ 5 mg/L (aOR 1.64, 95% CI 1.08–2.49), fibrinogen ≥ 3.5 g/L (1.55, 1.07–2.24), and B-Leu $> 9 \times 10^9$ cells/L (1.65, 1.10–2.47) remained associated.

Table 8. Association between blood-based inflammatory biomarkers and future AECOPD frequency in Paper III. Unadjusted ordinal logistic regression models. Each odds ratio represents a separate model.

Biomarker	n	OR	95 % CI
CRP, per 1 mg/L	565	1.02	0.99–1.04
CRP \geq 5 mg/L	565	1.86	1.29–2.67
Fibrinogen, per 1 g/L	545	1.59	1.26–2.00
Fibrinogen \geq 3.5 g/L	545	2.01	1.45–2.79
Leukocytes, per 1×10^9 cells/L	568	1.16	1.08–1.24
Leukocytes $> 9 \times 10^9$ cells/L	568	2.18	1.52–3.13
Platelets, per 100×10^9 cells/L	547	1.36	1.07–1.71
Platelets $> 350 \times 10^9$ cells/L	547	1.42	0.86–2.37
Neutrophils, per 1×10^9 cells/L	564	1.23	1.12–1.36
Neutrophils $> 5.4 \times 10^9$ cells/L	564	1.92	1.36–2.71
Lymphocytes, per 1×10^9 cells/L	562	0.90	0.73–1.11
Lymphocytes $\geq 1.8 \times 10^9$ cells/L	562	0.96	0.69–1.33
Monocytes, per 0.1×10^9 cells/L	562	1.10	1.03–1.18
Monocytes $> 0.8 \times 10^9$ cells/L	562	1.81	1.17–2.81
PLR, per 100 units	541	1.32	1.02–1.71
PLR ≥ 169.1	541	1.20	0.83–1.73
SII, per 100 units	541	1.08	1.04–1.12
SII ≥ 856	541	1.52	1.05–2.19
SIRI, per 1 unit	562	1.28	1.12–1.47
SIRI ≥ 2.024	562	1.76	1.23–2.52
AISI, per 100 units	541	1.09	1.04–1.14
AISI ≥ 533.7	541	2.03	1.40–2.92

Note: Bolded text indicates statistical significance at the 0.05 level (1 is not included in the 95% CI).

Abbreviations: OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation.

Paper IV

During the three-year follow-up of the 566 participants, the clinical COPD phenotypes displayed different AECOPD frequencies. The mean \pm SD frequencies were highest in phenotypes 1 (severe comorbid; 1.1 ± 1.8 per year) and 4 (very severe respiratory; 1.2 ± 1.8 per year) and lowest in phenotypes 3 (asymptomatic comorbid/obese; 0.2 ± 0.4 per year) and 5 (mild respiratory; 0.2 ± 0.4 per year), whereas phenotype 2 (mixed respiratory/comorbid) had an intermediate frequency (0.7 ± 1.2 per year) close to that of the total cohort (0.6 ± 1.2 per year). Figure 9 shows the Kaplan-Meier estimates of the cumulative probability of AECOPD for each phenotype.

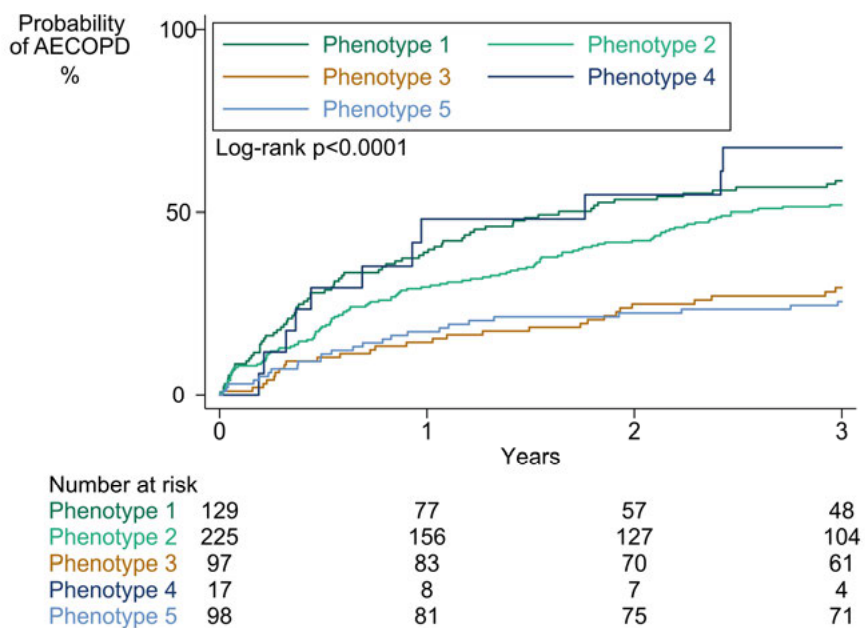


Figure 9. Kaplan-Meier graph showing the cumulative probability of AECOPD over three years in relation to clinical COPD phenotype in Paper IV. AECOPD, acute exacerbation of COPD.

Cox regressions (Table 9) indicated a 2–3 times higher risk of AECOPD in phenotypes 1 (severe comorbid), 2 (mixed respiratory/comorbid), and 4 (very severe respiratory) compared with phenotype 5 (mild respiratory), even after adjustment for AECOPD history (stratification variable), age, and current smoking. There were no statistical differences between phenotypes 1, 2, and 4, or between phenotypes 3 (asymptomatic comorbid/obese) and 5.

Table 9. The relative risk of future AECOPD in relation to clinical COPD phenotypes in the TIE study (Paper IV). Cox proportional hazards models of the association between clinical COPD phenotypes and AECOPDs. Participants were censored in the case of a competing event (death, n = 26) or at the end of the three-year follow-up.

Phenotype	Unadjusted (n = 566)		Adjusted* (n = 564)	
	HR	95% CI	aHR	95% CI
1, severe comorbid	3.04	1.93–4.79	2.09	1.29–3.39
2, mixed respiratory/comorbid	2.38	1.54–3.66	1.96	1.27–3.04
3, asymptomatic comorbid/obese	1.13	0.66–1.94	1.05	0.61–1.83
4, very severe respiratory	3.52	1.73–7.15	2.91	1.41–6.00
5, mild respiratory	ref		ref	

Notes: * Adjusted for AECOPD history the year before baseline (stratification variable), age, and current smoking at baseline. Data on smoking were missing for two participants. Bolded text indicates statistical significance (1 is not included in the 95% CI).

Abbreviations: AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio.

4.3 Biomarkers of systemic inflammation as outcomes

Blood-based biomarkers of inflammation were outcomes in Papers II and IV. In Paper II, the longitudinal stability of B-Eos and NLR was investigated, whereas in Paper IV, the association between clinical COPD phenotypes and several biomarkers was explored.

Paper II

There was a higher percentage of high NLR among participants with a history of AECOPD in the year before the baseline visit than in those without such history. For B-Eos, there was no such difference.

The intraclass correlation coefficient for stable-phase NLR was 0.61 (95% CI 0.56–0.66). During the study period, 40% had at least one high NLR measurement. Figure 10 shows that 11% had persistently high and 61% persistently low NLR, whereas 28% changed groups between visits.

The ICC for stable-phase B-Eos was 0.69 (95% CI 0.64–0.73). During the study period, 42% had at least one high B-Eos measurement. Figure 11 shows that 15% had persistently high B-Eos, 11% had persistently intermediate B-Eos, and 22% had persistently low B-Eos, whereas the remaining 52% changed groups between visits.

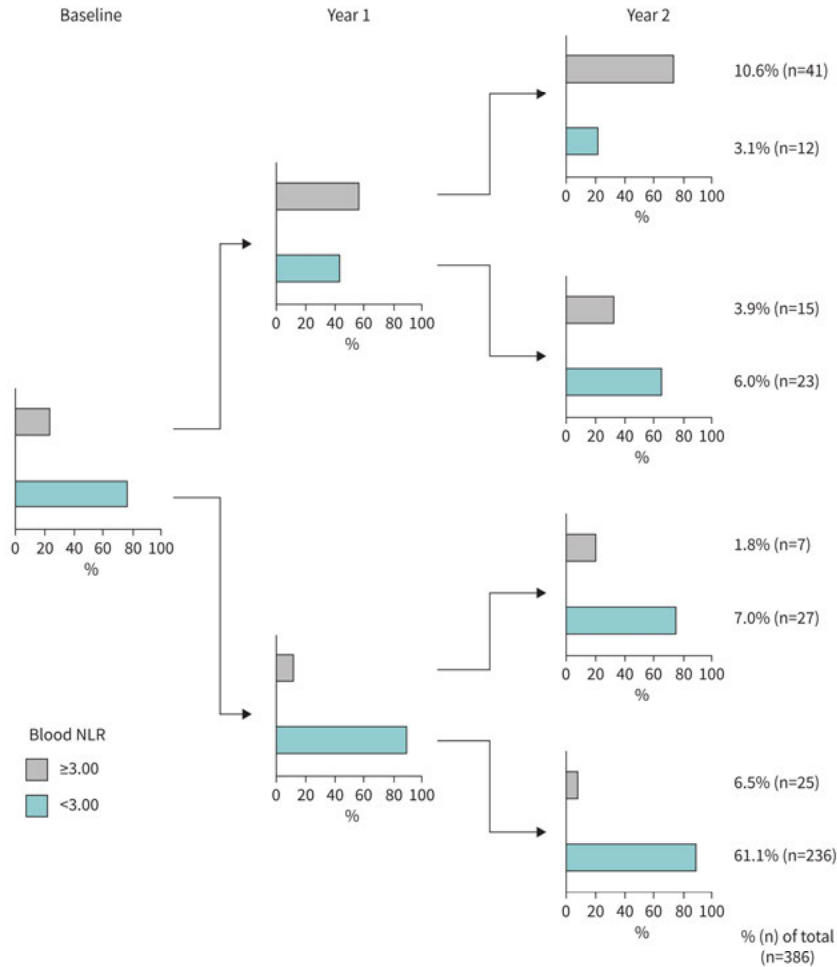


Figure 10. Longitudinal stability of blood neutrophil-to-lymphocyte ratio (NLR) in 386 participants in Paper II. The diagram on the left shows the proportion of subjects with high and low NLR at baseline visits. The diagrams in the middle show the respective proportions for year 1, and the diagrams on the right show the respective proportions for year 2. COPD: chronic obstructive pulmonary disease. Reproduced under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0 from Ellingsen J, Janson C, Bröms K, *et al.* Neutrophil-to-lymphocyte ratio, blood eosinophils and COPD exacerbations: a cohort study. *ERJ Open Res.* Oct 2021;7(4):00471-2021.

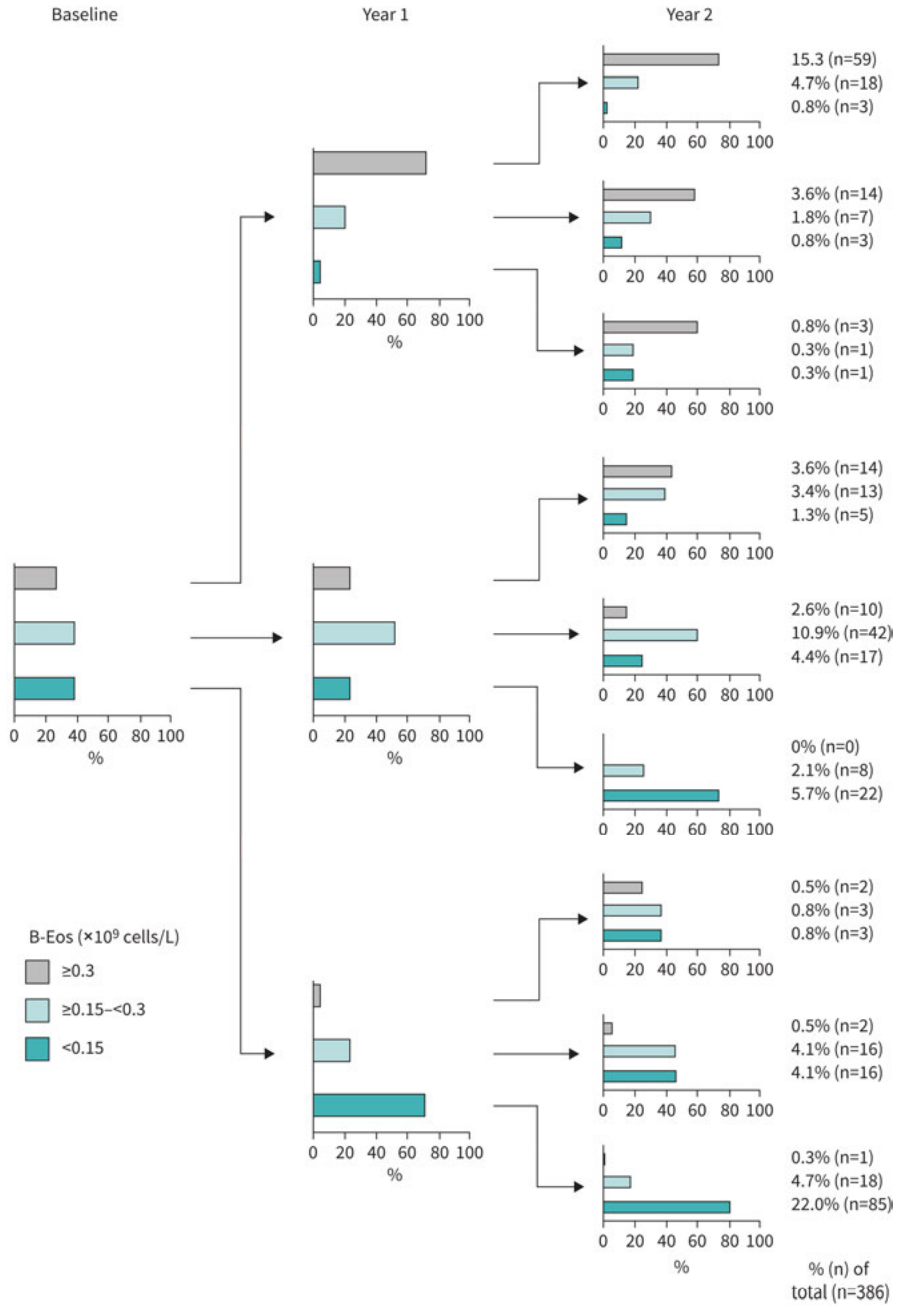


Figure caption, see next page.

Figure 11 (previous page). Longitudinal stability of blood eosinophil (B-Eos) levels in 386 participants in Paper II. The diagram on the left shows the proportion of subjects with high, intermediate, and low B-Eos at baseline visits. The diagrams in the middle show the respective proportions for year 1, and the diagrams on the right show the respective proportions for year 2. COPD: chronic obstructive pulmonary disease. Reproduced and adapted under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0 from Ellingsen J, Janson C, Bröms K, *et al.* Neutrophil-to-lymphocyte ratio, blood eosinophils and COPD exacerbations: a cohort study. *ERJ Open Res.* Oct 2021;7(4):00471-2021; compared with the original version, the unit and scale of B-Eos have been changed from cells/ μ L to $\times 10^9$ cells/L.

Paper IV

In the TIE study, the percentage of participants with high levels of blood-based biomarkers of inflammation differed between clinical COPD phenotypes (Table 10). In phenotype 1 (severe comorbid), the percentage with high levels was above the average for the entire study population for nearly all biomarkers.

There were associations between phenotypes and several inflammatory biomarkers in the logistic regression models, even after adjustment for AECOPD history, age, sex, and current smoking (Table 11). For CRP, the odds of having elevated levels were higher in phenotypes 1–4 than in phenotype 5. For fibrinogen, the odds of having elevated levels were higher in phenotypes 1 and 4 than in phenotype 5. For B-Leu, the odds were higher in phenotypes 1–3 than in phenotype 5. For B-Neu, B-Lym, B-Mon, SIRI, and AISI, the odds were higher in phenotypes 1 and 3 than in phenotype 5. Over all, the phenotypes most often associated with elevated inflammatory biomarkers were phenotypes 1 and 3.

Table 10. Participants in Paper IV with high levels of baseline blood-based biomarkers of inflammation in the total study population and each clinical COPD phenotype, n (%). Red colour indicates a higher proportion with high levels than in the total population, while green colour indicates a lower proportion with high levels.

	Total n = 566	Phenotype					p-value
		1 Severe comorbid n = 129	2 Mixed respira- tory/comorbid n = 225	3 Asymptomatic comorbid/obese n = 97	4 Very severe respiratory n = 17	5 Mild respiratory n = 98	
Platelets > 350*	58 (11%)	20 (17%)	20 (9%)	5 (5%)	1 (6%)	12 (13%)	0.067
Leukocytes > 9*	135 (24%)	51 (40%)	51 (23%)	21 (22%)	2 (12%)	10 (10%)	< 0.001
Neutrophils > 5.4*	165 (30%)	55 (44%)	63 (28%)	27 (28%)	4 (24%)	16 (17%)	< 0.001
Eosinophils ≥ 0.3*	147 (26%)	35 (28%)	56 (25%)	27 (28%)	2 (13%)	27 (28%)	0.70
Lymphocytes ≥ 1.8*	356 (64%)	83 (66%)	144 (65%)	68 (70%)	7 (44%)	54 (57%)	0.15
Monocytes > 0.8*	85 (15%)	35 (28%)	25 (11%)	19 (20%)	1 (6%)	5 (5%)	< 0.001
Basophils ≥ 0.09*	151 (27%)	34 (27%)	57 (26%)	32 (33%)	2 (13%)	26 (27%)	0.45
NLR ≥ 3.1	137 (25%)	45 (36%)	42 (19%)	26 (27%)	5 (31%)	19 (20%)	0.007
PLR ≥ 169.1	133 (25%)	31 (26%)	48 (22%)	25 (26%)	5 (33%)	24 (26%)	0.79
SII ≥ 856	134 (25%)	43 (37%)	43 (20%)	24 (25%)	5 (33%)	19 (20%)	0.010
SIRI ≥ 2.024	138 (25%)	50 (40%)	45 (20%)	27 (28%)	5 (31%)	11 (12%)	< 0.001
AISI ≥ 533	134 (25%)	50 (43%)	45 (21%)	23 (24%)	4 (27%)	12 (13%)	< 0.001
CRP ≥ 5 mg/L	134 (24%)	46 (36%)	54 (24%)	22 (23%)	5 (29%)	7 (7%)	< 0.001
Fibrinogen ≥ 3.5 g/L	297 (55%)	88 (72%)	114 (53%)	42 (45%)	13 (81%)	40 (43%)	< 0.001

Notes: Bolded p-values indicate statistical significance. * ×10⁹ cells/L.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation; CRP, C-reactive protein.

Table 11. Multivariable logistic regressions of the associations between clinical COPD phenotypes and dichotomised blood-based biomarkers of inflammation in Paper IV, adjusted for AECOPD history, age, sex, and current smoking.

Outcome	n	Phenotype 1 vs 5		Phenotype 2 vs 5		Phenotype 3 vs 5		Phenotype 4 vs 5	
		aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Platelets > 350*	541	1.22	0.52–2.86	0.68	0.31–1.48	0.41	0.13–1.28	0.45	0.05–3.82
Leukocytes > 9*	562	6.56	2.92–14.7	2.50	1.19–5.25	3.00	1.26–7.15	1.29	0.25–6.68
Neutrophils > 5.4*	558	3.78	1.86–7.68	1.76	0.94–3.32	2.20	1.04–4.68	1.51	0.41–5.54
Eosinophils ≥ 0.3*	556	0.92	0.48–1.75	0.77	0.44–1.34	0.83	0.43–1.63	0.32	0.07–1.55
Lymphocytes ≥ 1.8*	556	1.99	1.09–3.63	1.57	0.94–2.60	2.44	1.29–4.63	0.74	0.25–2.21
Monocytes > 0.8*	556	6.24	2.23–17.5	2.03	0.74–5.51	3.98	1.36–11.6	1.06	0.11–9.90
Basophils ≥ 0.09*	556	0.95	0.49–1.82	0.91	0.52–1.59	1.09	0.56–2.12	0.34	0.07–1.64
NLR ≥ 3.1	556	1.50	0.76–2.96	0.75	0.40–1.40	1.27	0.62–2.61	1.40	0.42–4.70
PLR ≥ 169.1	535	0.81	0.41–1.59	0.82	0.46–1.46	0.90	0.45–1.78	1.23	0.37–4.04
SII ≥ 856	535	1.57	0.79–3.13	0.81	0.43–1.51	1.21	0.59–2.51	1.56	0.46–5.31
SIRI ≥ 2.024	556	3.63	1.67–7.90	1.50	0.73–3.11	2.65	1.17–6.01	2.73	0.75–9.89
AISI ≥ 533	535	4.29	1.98–9.28	1.49	0.73–3.03	2.28	1.00–5.16	2.17	0.57–8.34
CRP ≥ 5 mg/L	559	8.76	3.55–21.6	4.22	1.82–9.77	4.88	1.89–12.6	6.50	1.72–24.5
Fibrinogen ≥ 3.5 g/L	539	3.93	2.12–7.27	1.53	0.93–2.53	1.39	0.75–2.58	6.90	1.80–26.4

Notes: Bolded text indicates statistical significance (1 is not included in the 95% CI). * $\times 10^9$ cells/L.
Abbreviations: vs, versus; aOR, adjusted odds ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation; CRP, C-reactive protein.

5 Discussion

5.1 Main findings and implications

In the four works included in this thesis (Figure 12), we have identified several risk factors for mortality (Paper I) and AECOPD (Papers II and III), and have shown that an algorithm using five pieces of information readily available in clinical practice allocates COPD patients to clinical phenotypes that are prognostic of mortality and AECOPDs (Paper IV).

People with COPD live with the risk of adverse outcomes such as AECOPD and premature death. Prevention of such events is a major goal for healthcare providers and respiratory researchers. A step in that direction is to identify those at highest risk, which has been the focus of this thesis. Better prognoses are helpful for patients wanting to know their risk, for healthcare providers in identifying patients needing greater attention or intensified treatment, and for policymakers in designing guidelines and allocating resources.

The co-occurrence of comorbidities such as heart diseases, diabetes, and stroke is a strong signal that a COPD patient has an increased risk of death (Papers I and IV) and that all measures to reduce risk should be taken.

As for the prognostic properties of the blood-based inflammatory biomarkers studied in this thesis (Papers II and III), none of them are mature for clinical use. However, NLR, CRP, fibrinogen, and B-Leu are prognostic of AECOPDs and deserve further investigation. More specifically, they should be analysed as parts of composite risk evaluation tools. For instance, the value of adding one or several of them to the ACCEPT online risk prediction tool could be analysed.¹⁵⁵

The algorithm for clinical phenotyping originally proposed by Burgel *et al.* incorporates information on comorbidities (heart failure, coronary artery disease, hypertension, and diabetes), dyspnoea as measured with the mMRC dyspnoea scale, lung function (FEV₁), age, and obesity (BMI). We have confirmed the algorithm's ability to identify COPD patients with increased mortality risk, and for the first time have shown that it can predict AECOPDs, although clinical use is discouraged for the latter purpose, pending validation.

Another aspect is that knowledge of factors associated with adverse outcomes may inform etiological research to unravel the pathological mechanisms leading to the disease, perhaps with the ultimate goal of new treatment targets. However, such research requires methods other than those applied in

the present work, and accordingly, this thesis makes no claims on having identified causal relationships between the factors studied.

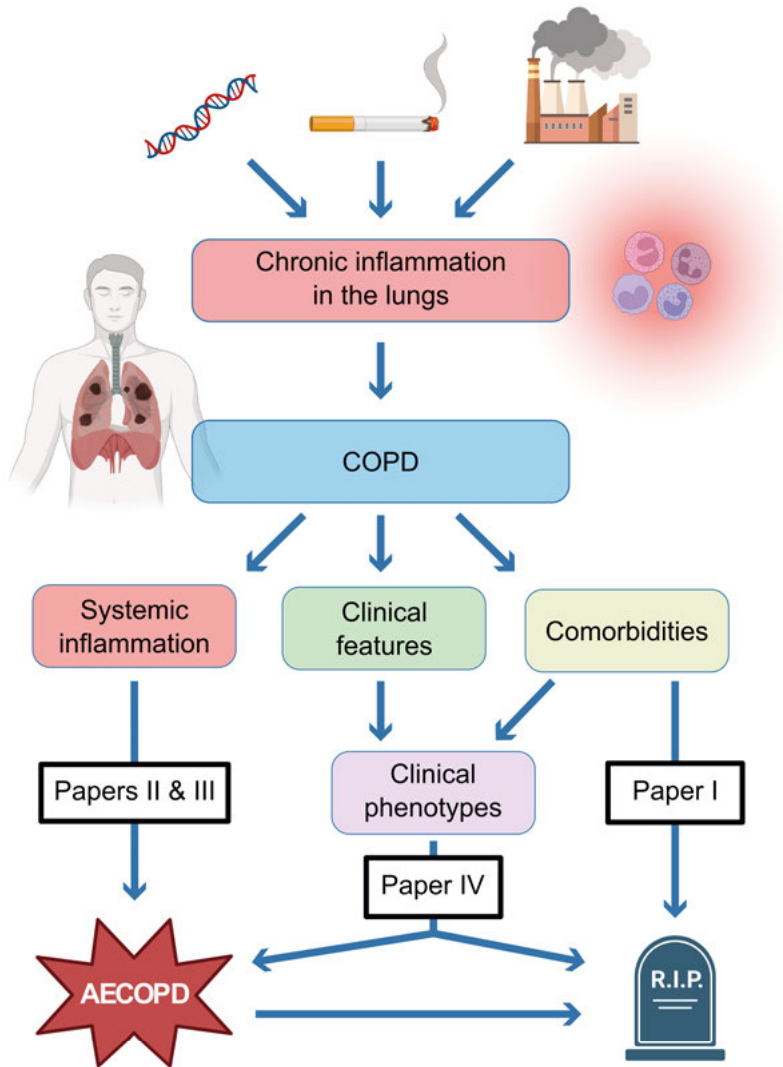


Figure 12. Schematic illustration of the works constituting this thesis. Created with BioRender.com

5.2 Methodological considerations

All works included in this thesis were observational, aiming to identify risk factors for adverse outcomes in COPD. The studies were not designed for causal inference.

5.2.1 PATHOS

The PATHOS study, forming the basis for Paper I, was a population-based retrospective cohort study using primary care medical record data combined with data from mandatory national registers. This approach enabled the collection of a large study population with data on many potential risk factors. Moreover, it ensured a thorough follow-up with a minimal loss to follow-up thanks to the mandatory Cause of Death Register. PATHOS aimed to be representative of the entirety of Sweden by including data from healthcare centres in various settings (e.g., urban and rural areas, different Swedish regions, private and public healthcare providers); those healthcare centres covered about 8% of the Swedish population.

However, PATHOS and Paper I suffered from some limitations. First, COPD was defined based on ICD-10 codes, and the diagnosis was not confirmed through spirometry. This means that individuals with other diagnoses, e.g., asthma, may have been misclassified as having COPD and vice versa. The lack of confirmation of the diagnosis is a limitation that applies to all comorbidities included in Paper I. Second, there were spirometry data for only a minority of the population, so we could not adjust our analyses for the severity of airflow obstruction, a significant risk factor for COPD mortality.⁵⁹ Similarly, there were data on smoking history, also a significant risk factor,⁹ for only a minority. Data on BMI and vaccination status were also lacking.^{150,265,266} Third, analyses of pharmacological treatment may be subject to several kinds of bias, including residual confounding bias (factors not being adjusted for in the analysis, especially such that may constitute an indication for the drug of interest), collider bias (stratification by or adjustment for a factor that is a cause of both the exposure and the outcome),¹³⁸ and prevalent user bias (the study measures the effect of already being a user of the drug, not of initiating the treatment, i.e., those quitting the drug, or even dying due to adverse events will be excluded from the analysis, a sort of selection bias).²⁶⁷ Measures were taken to avoid immortal time bias (registration of outcome events starting at a later timepoint than inclusion in the study, i.e., participants staying in the study during a time period in which no event can occur).¹³⁹ Furthermore, there may be confounding by indication (the reason that the drug is prescribed is what confers the risk of an outcome), which can produce overly negative associations.

Despite these limitations, PATHOS contributed substantial real-world evidence on a large primary care cohort that was probably representative of the Swedish population.

5.2.2 TIE

Papers II–IV were based on the TIE cohort study, including patients with a COPD diagnosis. The diagnosis was confirmed through spirometry, and the

participants were invited to three yearly visits during a stable phase of COPD. A thorough assessment was made with a range of study procedures at each visit. This provided detailed information on most aspects of the participants' COPD-related health. Moreover, the study design offered longitudinal data with repeated measurements of various parameters, allowing for, e.g., stability analyses.

In Paper II, the primary outcome of AECOPDs was based on the questionnaires filled in by the participants. This approach had some drawbacks, such as the inability to count the number of AECOPDs due to the design of the questionnaire (resulting in a low-resolution binary outcome), no information on dates of events (precluding time-dependent analyses such as Cox proportional hazards regressions), no data on the outcome after the third visit, and no data on participants not attending follow-up study visits. Self-reported information is also subject to a significant amount of recall bias.

Therefore, in Papers III and IV, the follow-up was performed with an alternative approach, where medical records were reviewed for AECOPDs during the study period. Electronic medical record systems, to which most healthcare centres, hospitals, and other healthcare providers in each region are connected, ensured that the vast majority of the AECOPDs was recognised. Additionally, thanks to the automatic linkage between medical records systems and the mandatory governmental population register (*Folkbokföringen* in Swedish), deaths occurring during the follow-up period were also registered through the medical record review.

The medical record review process has limitations. There is a risk that AECOPDs were missed, for instance, if they were not properly labelled or described in the medical records. Self-treated events, where the participant never contacted healthcare, were not registered. In Sweden, each region has its own medical record system. These systems do not automatically transfer information to the systems of other regions; therefore, if a participant experienced an AECOPD when travelling in another region, that event was not recognised. The same applies to travels abroad.

Nonetheless, medical record reviews were suited for our analyses in Papers III and IV, as they offered the possibility to count AECOPDs, do time-dependent analyses, and produce a longer and more complete follow-up with data up to three years after baseline for all participants who attended baseline visits.

There were some other limitations to the TIE study. Comorbidities and pharmacological treatment were self-reported only and may have been subject to misconceptions and recall bias. Data on respiratory tract infections and GERD – known risk factors or triggers of AECOPDs – were lacking.^{71,268,269} There was only a small proportion of participants with very severe COPD in TIE, and in Paper II, the subpopulation studied had less severe COPD than those not included, making it difficult to generalise our findings to patients with GOLD grade 4 COPD. Measuring an inflammatory blood-based biomarker at a single time point, as in Papers III and IV, may not be

representative of that individual, as levels may be affected by residual inflammatory activity from, e.g., a previous AECOPD. However, if there had been an AECOPD, the study visit was postponed until four weeks after the latest event, and even further for participants who did not feel well at the time of the visit. Lastly, three different labs with different equipment were used for the laboratory analyses. Moreover, in some cases, the equipment was changed during the course of the study.

5.3 Mortality

In Paper I, real-world data were used to identify factors associated with mortality in a large population-based cohort of Swedish primary care COPD patients. At the time of writing the manuscript, only a few reports on COPD mortality utilising real-world data had been published,^{66,74,270,271} and Paper I was a substantial contribution.

In Paper IV, we confirmed that the algorithm initially proposed by Burgel *et al.*¹⁴⁹ can predict three-year mortality.

5.3.1 Comorbidities and COPD mortality

Comorbid heart disease, including HF, MI and IHD, was among the strongest predictors of mortality in Paper I. Several observational studies have shown a relationship between heart disease and mortality in COPD,^{52,63,73,74,270-273} although a few studies report contradicting results.²⁷⁴ A meta-analysis published in 2020 concluded that comorbid HF increases COPD mortality,⁷⁶ whereas a 2021 meta-analysis concluded that comorbid COPD increases HF mortality.²⁷⁵ In the quoted studies, the coexistence of heart disease was assessed in different ways, and the study populations were heterogeneous. Despite these differences, the results are quite homogeneous and confirm that HF and IHD are important risk factors for COPD mortality.

Stroke was associated with increased mortality in Paper I, in accordance with some previous reports,^{63,270} but not all.⁶⁶ Stroke and COPD both confer high mortality, and their coexistence may be an instance of the multimorbidity phenomenon where people with several diagnoses have a higher risk of adverse outcomes.⁷⁷ Indeed, the CCI was associated with increased mortality in Paper I. Diabetes is a strong risk factor for cardiovascular complications, and the increased mortality risk associated with it in Paper I has also been reported by others.²⁷⁶

Hypertension was related to decreased mortality in the adjusted Cox regression in Paper I. That association is clinically highly unlikely, as hypertension is a cause of, e.g., cardiovascular diseases and a well-described risk factor for premature death.²⁷⁷ A more probable explanation is that hypertension – like many other comorbidities – is underdiagnosed in COPD,²⁷⁸ i.e., when a

diagnosis is established, treatment is initiated that lowers the mortality risk compared with for those with unrecognised hypertension classified as non-hypertensive. This may also apply to depression, where no association to mortality was found in Paper I, contrary to other reports.²⁷⁹

Asthma at baseline was associated with decreased mortality in Paper I. Previous reports on the relation between comorbid asthma and COPD mortality have shown conflicting results,^{83,84} although the majority are in accordance with ours.⁸⁰⁻⁸² COPD patients with comorbid asthma seem to have a better prognosis than those without. This may be explained by different pathobiological mechanisms in the etiotypes COPD-A (COPD due to asthma) and COPD-C (COPD due to smoking). Another potential explanation is misclassification of patients with asthma as having COPD.

5.3.2 The phenotyping algorithm for mortality prediction

In Paper IV, the algorithm (Figure 7, page 43) initially proposed by Burgel *et al.*¹⁴⁹ predicted three-year mortality. The mortality risk was highest in phenotypes 4 (very severe respiratory), 1 (severe comorbid), and 3 (asymptomatic comorbid/obese). Phenotype 4 had the numerically highest mortality risk, but was statistically indistinguishable from phenotypes 1 and 3. However, the subpopulation in phenotype 4 was small ($n = 17$), and there is a separation of the Kaplan-Meier curves, so we deemed it likely that there was a difference. Our results aligned with those in the original publication of Burgel *et al.*¹⁴⁹ and two subsequent validation studies.^{151,152}

Notably, adjustment for AECOPD history did not alter the results significantly. AECOPD history is subject to various errors, such as difficulties identifying AECOPDs in medical records, patient recall bias, and difficulties in the history-taking defining the outcome (what constitutes an AECOPD?). Our results showed that omitting AECOPD history did not decrease accuracy significantly. Without it, we have an algorithm that uses relatively objective and easily accessible information.

This work, together with the original publication and subsequent validation studies,^{149,151,152} clearly shows that the algorithm can identify COPD patients with increased mortality risk, at least in predominantly Caucasian populations. Future research should validate its usefulness in non-Caucasian populations, compare its performance with other risk prediction tools, e.g., the BODE index, and seek to translate the relative risk increase to absolute risk measures, to provide patients and healthcare providers with more concrete information.

5.3.3 Pharmacological treatment and COPD mortality

In Paper I, associations between the use of several drugs and mortality were analysed. A higher number of defined daily doses of LAMAs and NAC per day were related to increased mortality. In contrast, more doses of ICS, beta-

blockers, ASA, and SSRIs were related to decreased mortality. However, observational studies on outcomes associated with pharmacological treatment should always be interpreted cautiously as subsequent RCTs often arrive at contradicting conclusions.^{141,142,280}

The associations of LAMAs and NAC with increased mortality found in Paper I may be confounding by indication, as we could not, due to lack of data, adjust for impaired lung function and chronic bronchitis. The associations in Paper I of ICS, beta-blockers, ASA, and SSRIs with decreased mortality are susceptible to prevalent user bias.²⁶⁷

However, regarding ICS, our results align with recent large-scale RCTs' finding that ICS improve survival among highly symptomatic COPD patients with a significant AECOPD history.¹²⁹

Previous observational studies on beta-blockers have indicated an association with improved survival in COPD.¹³⁵ However, a critical review has identified several sources of bias that may have exaggerated the results.¹³⁹ The only published RCT on people with COPD and no approved indication for beta-blockers showed no benefit; instead, it found that metoprolol appeared to increase AECOPD hospitalisations and that mortality was numerically higher in the metoprolol group.¹⁴² Our results aligned with those of previous observational studies and – pending results from future RCTs²⁸¹ – should not be overemphasised.

As regards ASA, there are no published RCTs on mortality in COPD patients lacking an approved indication. The potential role of platelets in the pathobiology of COPD is a theoretical rationale for antiplatelet drugs.¹⁹¹ Previous observational studies have suggested benefits of ASA,^{136,282} but the results have been criticised.¹³⁸ A longitudinal study reported that COPD patients treated with ASA had a slower progression of emphysema than those without ASA.²⁸³ Taken together, these results mandate further, well-designed studies on ASA in COPD.

There is no pathobiological reason to believe that the association observed between SSRIs and decreased mortality is a direct effect of the drug class on COPD, although an RCT has shown increased quality of life and exercise capacity in people with COPD and on SSRIs.²⁸⁴ A more plausible explanation is that adequate treatment of otherwise underdiagnosed and undertreated mental illnesses²⁸⁵ among people with COPD leads to a better prognosis, possibly by improving adherence to other pharmacological and non-pharmacological therapies, improving physical activity, and reducing the risk of suicide.²⁸⁶

Although there are few studies designed to examine the effects of treatment of comorbidities specifically in COPD, treatment should be pursued as indicated. This is particularly important regarding concomitant heart diseases.^{13,287,288} Our results emphasise that comorbidities are a signal of a patient at significant risk of adverse outcomes and that clinical management of COPD should include cardiac assessment and treatment.

5.4 Acute exacerbations of COPD

5.4.1 Biomarkers

In Papers II and III, we demonstrated that NLR, B-Eos, CRP, fibrinogen, and B-Leu were associated with a higher risk of future AECOPDs. However, the increases in relative risk were generally not large. On the other hand, PLR, SII, SIRI, and AISI were not associated with future AECOPDs.

NLR was associated with about 20% increased risk of AECOPD per unit increase, after adjustment for confounders. A few previous Asian cohorts of predominantly male COPD patients have found that NLR can predict AECOPDs.^{116,193,254-256} Our results add to the literature showing that stable-phase NLR is prognostic of AECOPDs, and, importantly, that this association is valid in a North European population. However, the magnitude of the association was small in our work. A question for future research is whether NLR is of greater value in COPD patients with a history of AECOPD than in those without.

Regarding B-Eos, levels $\geq 0.3 \times 10^9$ cells/L were associated with about 50% increased AECOPD risk. Previous results on the prognostic properties of B-Eos are inconsistent. Some studies report findings similar to ours,²⁰⁹⁻²¹⁵ and others report no association or weak associations between B-Eos and AECOPD.²¹⁶⁻²²⁴ These differences may be explained by different B-Eos cut-offs being used, and different confounders being accounted for. Moreover, within-day and between-day variability of B-Eos may affect study results.²³⁴ Although systematic reviews favour a prognostic role of B-Eos for AECOPDs,⁵⁸ the lack of a consistent signal shows that B-Eos is not ready for clinical use as a prognostic biomarker. Further prospective, large-scale studies with rigorous methodology are needed to establish whether B-Eos are clinically useful for AECOPD prediction.

Participants with baseline CRP ≥ 5 mg/L had a 60% risk increase for higher AECOPD frequency than those with lower CRP. This finding is in line with previous results.^{99,108,168,169,175-179} However, previous studies have found that CRP is associated with AECOPDs in the unadjusted analyses only,^{99,169,175} when analysed together with other biomarkers^{168,179} or only with regard to severe AECOPDs.¹⁷⁶⁻¹⁷⁸ Thus, our was the first study to show an independent association between CRP and total AECOPDs; the use of dichotomised CRP is a likely reason for this finding. Other reasons that previous studies did not find independent associations with total AECOPD include that only severe AECOPD was the outcome in two studies,^{176,177} and that inclusion was restricted to participants with an FEV₁ $\geq 50\%$ and $\leq 70\%$ predicted in one study.¹⁷⁸ To conclude, CRP seem to be prognostic of AECOPDs, but more work is needed to establish this association and elucidate whether its use has a clinical benefit.

Fibrinogen ≥ 3.5 g/L was associated with a 50% increase in AECOPD risk after adjustment for confounders, in accordance with previous results.^{108,181-184} Others have found fibrinogen to be associated with AECOPDs in unadjusted analyses only,^{99,169} or with severe AECOPDs only.^{178,185} Moreover, fibrinogen analysed in combination with other biomarkers is prognostic of AECOPDs.^{168,179} In summary, the evidence from our work and that of others indicates that fibrinogen ≥ 3.5 g/L is independently prognostic of future AECOPDs. Future analyses should examine if incorporating fibrinogen in composite tools enhances predictions.

B-Leu $> 9 \times 10^9$ cells/L were associated with a 65% increase in AECOPD risk. This aligns with two previous reports, although they used continuous B-Leu.^{99,185} Others have reported associations only in unadjusted analyses.^{175,193} A meta-analysis including three studies found no association between B-Leu and future AECOPD.¹⁰⁸ However, B-Leu analysed in combination with other biomarkers have been shown to predict AECOPDs.^{168,179} Over all, there are encouraging indications regarding stable-phase B-Leu as a predictor of AECOPDs, but confirmation in further studies is needed.

In Paper III, none of the four blood cell indices (PLR, SII, SIRI, and AISI) studied was independently associated with AECOPDs. AISI has, to our knowledge, never before been studied in relation to future AECOPD, whereas PLR, SII, and SIRI were found to be associated with future AECOPD in one study.²⁵⁸ However, that study did not adjust for the strongest risk factor: AECOPD history.⁵⁸ PLR is higher in AECOPD than in stable COPD,¹⁹⁰ and previous AECOPDs are associated with higher B-Plt.²⁸⁹ The fact that we adjusted for AECOPD history probably explains why we found no association between the indices and future AECOPDs. Our results regarding PLR, SII, SIRI, and AISI measured during stable-phase COPD are discouraging; these indices seem to be of limited value in predicting AECOPDs.

The results of this thesis and other works indicate that the additive predictive power regarding AECOPDs of the studied biomarkers is generally small. However, a slight improvement is still an improvement. Adding biomarkers may trim an existing prediction tool from good to better.¹⁵⁵ Moreover, a prediction model may be simplified if it is found that biomarkers can replace other factors. Many blood-based biomarkers are relatively objective compared with history-taking. The biomarkers studied in this thesis are widely available and typically easy to obtain; they may even have been sampled on previous occasions and be ready for use. On the other hand, in many cases, biomarkers – especially blood-based biomarkers – have a cost that must be considered before deciding to implement them in clinical routine. Nonetheless, the example of B-Eos as a predictive biomarker of response to ICS treatment shows that COPD care can be improved by studying biomarkers.

5.4.2 Clinical characteristics – the phenotyping algorithm

In Paper IV, we found an association between the clinical COPD phenotypes identified by the algorithm developed by Burgel *et al.* for mortality prediction,¹⁴⁹ and future AECOPDs in time-to-event analyses. The items included in the algorithm are established risk factors for AECOPDs,⁵⁸ although regarding BMI, being underweight is probably a stronger risk factor than having a BMI < 30 kg/m²,^{58,290} the cut-off used in the algorithm.

The phenotypes with the highest risks were 1 (severe comorbid), 2 (mixed respiratory/comorbid), and 4 (very severe respiratory). Although phenotype 4 had a numerically higher estimate, there was no statistically significant difference between these three phenotypes. However, only 17 participants were allocated to phenotype 4, and the Kaplan-Meier curves separated; therefore, we speculated that a study population with a higher proportion of more severe COPD, i.e., with more individuals with phenotype 4, would reveal differences. In light of the strong associations between severely impaired FEV₁ and cardiovascular disease, respectively, and AECOPD,⁵⁸ it is unsurprising that phenotypes 1 and 4 had higher risks of AECOPDs than phenotypes 3 and 5.

Interestingly, despite AECOPD history being the strongest risk factor for future AECOPDs,⁵⁸ adjustment for it did not significantly change our estimates. A risk prediction tool independent of AECOPD history may prove clinically useful, as that variable is subject to patient recall bias and may be difficult to identify in healthcare records.

Other AECOPD risk prediction tools exist, but none is recommended by GOLD, except simply obtaining AECOPD history.¹³ ACCEPT seems closest to clinical acceptance and has the advantage of individual risk prediction through statistical calculations.^{153,155} However, its use depends on internet access and a web application, and 13 items must be entered. On the other hand, the clinical phenotyping algorithm needs only five pieces of information and is very easy to use; you might not even need a pen. Thus, the algorithm can potentially become a clinically valuable alternative to ACCEPT, provided that our results are validated in future studies.

The phenotypes with the highest risk of AECOPD only partially overlapped with those with the highest mortality risk. Phenotypes 1 (severe comorbid) and 4 (very severe respiratory) had a high risk of both. In contrast, phenotype 2 (mixed respiratory/comorbid) had a high risk of AECOPD only, and phenotype 3 (asymptomatic comorbid/obese) had a high risk of mortality only. The composition of the algorithm may explain this. Participants with impaired FEV₁ (associated with increased AECOPD risk), but without significant dyspnoea, will likely be allocated to phenotype 2, whereas those in phenotype 3 will to a large degree be characterised by the combination of comorbidities, obesity, and high age, i.e., strong risk factors for mortality.⁵²

5.5 Biomarkers of systemic inflammation as outcomes

Although not the main focus of this thesis, biomarkers served as outcomes in some analyses. The longitudinal stability of NLR and B-Eos was studied in Paper II. The associations between clinical phenotypes and several biomarkers were investigated in Paper IV.

5.5.1 Longitudinal stability of NLR

In Paper II, 11% of the participants had persistently high NLR values (≥ 3). The ICC was 0.61, which is regarded as fair longitudinal reliability.²³⁸ This was the first study to analyse the ICC of repeated stable-phase NLR measurements in a pure COPD population. One previous study of a mixed population about to undergo cardiac surgery included 15 participants with unspecified lung disease and reported an ICC of 0.59.²⁹¹ Another study found that the median change in NLR was 0.05 per year.²⁵⁶ Our results need confirmation in future studies but indicate that NLR is reasonably stable over time in stable COPD. A single measurement is, therefore, likely to be representative for that individual. The lack of an established cut-off for high NLR hampered our results.

5.5.2 Longitudinal stability of B-Eos

About 15% had persistently high ($\geq 0.3 \times 10^9$ cells/L) B-Eos in Paper II, and 22% had persistently low ($< 0.15 \times 10^9$ cells/L) values. The ICC was 0.69, which is regarded as good reliability.²³⁸ These findings align with other reports, where persistently high B-Eos have been found in approximately 20% of the cohorts,^{217,223,235-237} and ICCs of around 0.8 have been reported.^{236,238,239} Two reports have yielded other results regarding the proportion of patients with persistently elevated B-Eos: 45% and 5%, respectively.^{292,293} In the former study, the high number may have resulted from the AECOPD history being assessed at baseline only, meaning that subsequent samplings may have been drawn during or close to an AECOPD.²⁹² The latter study had a lower proportion of participants with high B-Eos at baseline than our study (15% versus 27%) and a lower proportion of participants with comorbid asthma.²⁹³ Taken together, the evidence indicates that B-Eos is at least fairly reliable as a biomarker, although there is some between-day variability. Adding to that is the within-day variability observed in other studies, indicating that the time of day for blood sampling significantly impacts B-Eos.²³⁴ The time of blood sampling should be noted and considered when interpreting B-Eos results in the clinical setting.

5.5.3 Inflammatory biomarkers and the phenotyping algorithm

In Paper IV, we investigated if the phenotypes produced by the algorithm developed by Burgel *et al.*¹⁴⁹ were associated with high levels of several blood-based inflammatory biomarkers. We found that in phenotype 1 (severe comorbid), a larger proportion of participants had elevated levels of nearly all the studied biomarkers compared with the population as a whole. In logistic regressions, phenotypes 1 and 3 (asymptomatic comorbid/obese) were associated with elevated levels of most biomarkers. It seems that age and comorbidities, including obesity, may explain much of this association.^{52,294,295} Phenotype 4 (very severe respiratory) had a small sample ($n = 17$), yet it was very clearly associated with CRP and fibrinogen. It is possible that a study population with more participants with severely impaired FEV₁ would have resulted in associations between phenotype 4 and more of the biomarkers, reflecting systemic inflammation as a feature of COPD.¹⁶⁸ This is the first study to examine differences in inflammatory patterns between the clinical phenotypes, despite the call from Burgel *et al.* for such investigations.¹⁴⁹ Future research should evaluate if one or more of the inflammatory biomarkers could substitute some of the information currently used in the algorithm, to produce a simpler-to-use or better-performing algorithm.

6 Conclusions

- I. Comorbidities, particularly heart diseases and stroke, are strong risk factors for COPD mortality and should be an integral part of the management of COPD patients. There is a need for further studies on the optimal pharmacological management of comorbidities in COPD.
- II. Eosinophils and neutrophil-to-lymphocyte ratio measured in blood during a stable phase of COPD can predict future AECOPDs and have fair longitudinal stability over three yearly measurements.
- III. CRP, fibrinogen, and blood leukocytes measured during a stable phase of COPD are independently prognostic of future AECOPDs. In contrast, the blood cell indices platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, and aggregate index of systemic inflammation are of limited value.
- IV. A previously developed algorithm for clinical phenotyping predicts mortality and AECOPDs. The phenotypes show different patterns of blood-based inflammatory biomarkers.

7 Future perspectives

Regarding mortality prediction, the algorithm initially developed by Burgel *et al.*¹⁴⁹ and further investigated in this thesis should be validated in, e.g., Asian cohorts. It is also necessary to compare its performance with those of other tools, such as the ADO and the BODE indices,^{144,146} to find out which performs best and is most straightforward to use. Whether the algorithm's performance can be enhanced by the addition of inflammatory biomarkers, such as CRP, fibrinogen, or B-Leu, merits some scientific effort. Likewise, the association of the phenotypes to various inflammatory profiles raises the question of whether the biomarkers could substitute other information to produce a simpler or more accurate algorithm.

Although the algorithm and other tools, such as the BODE index, can be used to identify patients with increased mortality risk, the risk estimates are relatively coarse and pertain to a group that may be quite heterogeneous. There is a need for improved predictions at the individual level. Therefore, future research should aim to develop a mathematical risk prediction tool for mortality, similar to the online web application ACCEPT for AECOPD prediction.¹⁵⁵ This process should consider all known risk factors of mortality, especially comorbid heart disease. Usability and cost-benefit are critical values for any clinical tool aiming to enter the healthcare system, which is strained in many countries. Therefore, ease of use and costs associated with using a biomarker, for instance, must be integral parts of the development of any such tool. Once in clinical use, it could be a valuable complement to the algorithm by giving more exact predictions at the expense of taking more time, whereas the algorithm identifies risk patients in seconds, but with coarse risk estimates.

Regarding pharmacological treatment, this thesis highlights some areas of COPD management that are still relatively unexplored. There is a lack of high-quality data on managing comorbidities in COPD. This pertains particularly to heart diseases due to the detrimental prognosis associated with them and their common undertreatment in COPD.^{296,297} Another group of comorbidities with insufficient information on treatment is psychiatric disorders, particularly anxiety and depression, known to cause high morbidity and lower quality of life in COPD. Existing data from previous RCTs, cohorts, and health databases/registers should be thoroughly investigated to elucidate the optimal treatment strategies as far as possible. In several cases, there may be a need for new, probably academic clinical trials explicitly investigating comorbidity

management in COPD. Pragmatic designs are needed to accomplish such trials – often with limited public funding – and to include real-world patients in them.

Data from observational studies, including ours, indicate a survival benefit for COPD patients using ASA. A mechanistic link between COPD and cardiovascular disease via activated platelets has been suggested.^{191,192} Some authors think current data are too weak for considering an RCT on ASA in COPD with no other indication for the treatment,¹³⁸ i.e., primary prevention of cardiovascular events. An emulated trial based on observational data could be considered.²⁸⁰ However, all observational studies, regardless of how rigorously they are performed, will be biased because there was a reason for the physician to initiate ASA in the first place, i.e., confounding by indication. Therefore, I would argue that the time is come for a clinical trial on the primary prevention of cardiovascular death in COPD with antiplatelet therapy.

Regarding AECOPDs, future research should seek to validate our finding that the algorithm proposed by Burgel *et al.*¹⁴⁹ can predict AECOPDs. Moreover, studies should investigate whether existing risk prediction tools, such as ACCEPT or the algorithm analysed in this thesis, can be improved by the inclusion of blood-based biomarkers such as NLR, B-Eos, CRP, fibrinogen, or B-Leu; it is also possible that the tools can be simplified if the biomarkers can substitute information currently used in them. However, that kind of study also mandates a cost-benefit analysis, as the blood-based biomarkers are often significantly more expensive to measure than other clinical data.

8 Sammanfattning på svenska – Summary in Swedish

Målet med denna avhandling har varit att undersöka faktorer som kan förutsäga försämringsepisoder och död hos patienter med kroniskt obstruktiv lungsjukdom (KOL). Ett särskilt fokus har legat på samsjuklighet, det vill säga förekomst av andra sjukdomar parallellt med KOL, och inflammatoriska biomarkörer. Det sistnämnda är blodprover som återspeglar graden av inflammatoriskt påslag i kroppen.

KOL är en vanlig sjukdom. Den beräknas drabba omkring 7% av alla vuxna svenskar. Dödligheten är högre hos personer med KOL än hos befolkningen i allmänhet. Förutom ökad risk för död kan KOL-patienten lida av andfåddhet, hosta, låg fysisk kapacitet, abnorm trötthet, avmagring, förlust av muskelmassa och låg livskvalitet. Risken för att drabbas av samsjuklighet är förhöjd jämfört med hos lungfriska; detta gäller i synnerhet för hjärt-kärlsjukdomar.

Den vanligaste och mest kända orsaken till KOL är tobaksrök, men sjukdomen kan också orsakas av till exempel luftföroreningar, matlagning inomhus över öppen eld (och drabbar då främst kvinnor i fattiga delar av världen), infektioner i lungorna eller ärftliga faktorer. KOL kännetecknas av lungemfysem – att lungblåsorna, alveolerna, förstörs och det i stället bildas större och mer ineffektiva hålrum i lungorna – och inflammation i de minsta luftvägarna, bronkiolerna. Dessa två faktorer förekommer i varierande grad hos olika patienter, och tillsammans orsakar de trånghet (obstruktion) i luftvägarna. Obstruktion förekommer även vid andra sjukdomar, som till exempel astma, men vid KOL normaliseras aldrig obstruktionen – den är kronisk. Luftvägsobstruktion kan man mäta med ett lungfunktionstest, en så kallad spirometri. För att ställa diagnosen KOL krävs vanligen spirometriresultat och symtom som stämmer med sjukdomen, och dessutom en orsak, som till exempel tidigare rökning.

Många KOL-patienter drabbas av försämringsepisoder, så kallade exacerbationer. En exacerbation är en tillfällig försämring av luftvägssymtomen, och utlöses ofta av en virus- eller bakterieinfektion. Det kan ta lång tid att återhämta sig efter en exacerbation, och den kan få många negativa följder som försämrad lungfunktion, sämre livskvalitet och ökad risk för förtida död. Dessutom ökar risken för en förnyad exacerbation, så att patienten riskerar att hamna i en negativ spiral. Det är därför väldigt viktigt att förebygga exacerbationer.

Den viktigaste behandlingen vid KOL är luftrörsvidgande inhalationsläkemedel, som mildrar luftvägsobstruktionen. Den som har drabbats av eller har ökad risk att drabbas av exacerbationer bör dessutom andas in ett kortisonpreparat. Vid en exacerbation ger man tillfälligt ökade doser av luftrörsvidgare, ofta i kombination med kortisonpiller och antibiotika.

För att kunna förebygga negativa händelser som exacerbationer och förtida död krävs kunskap om vilka faktorer som är förknippade med ökad risk att drabbas, vilket har varit målet med detta forskningsprojekt. Avhandlingen består av fyra delarbeten.

Delarbete 1 utgick från en anonymiserad databas med uppgifter om knappt 18 000 primärvårdspatienter med KOL från många olika delar av Sverige. Uppgifterna kom från patientjournaler och flera olika nationella register, som till exempel Dödsorsaksregistret och Läkemedelsregistret. Genom att kombinera dessa uppgifter kunde patienterna följas under flera års tid. Under uppföljningstiden inträffade många dödsfall. Utifrån databasen kunde vi analysera vilka faktorer som var förknippade med ökad eller minskad risk för död. De som hade samtidig hjärtsjukdom, stroke eller diabetes hade en högre risk att dö medan de med samtidig astma hade en lägre risk. En KOL-patient med samsjuklighet kan alltså behöva extra uppmärksamhet av vården.

Delarbete 2 undersökte om två inflammatoriska biomarkörer analyserade i blodprov kan förutsäga vilken KOL-patient som löper ökad risk att drabbas av exacerbationer. Här användes data från en studie som kallas TIE, där patienter med KOL inbjöds att delta vid tre årliga studiebesök. Patienterna rekryterades från primärvård och sjukhusvård i Dalarna, Gävleborg och Uppsala, och vid varje studiebesök genomgick de en lång rad undersökningar och fick besvara enkäter om sin hälsa. Till delarbete 2 kunde data från knappt 500 av deltagarna i TIE användas, och vi såg att det fanns kopplingar mellan de två biomarkörerna eosinofiler och NLR (kvoten mellan neutrofiler och lymfocyter) och att drabbas av exacerbationer under uppföljningen. Sambanden var dock relativt svaga, vilket tyder på att dessa biomarkörer inte ensamma är användbara, men kanske kan vara det om de kombineras med andra faktorer i ett prognosverktyg.

Delarbete 3 utgick även det från TIE-studien och undersökte om sju andra biomarkörer kunde användas för att förutspå framtida exacerbationer. Här valde vi en lite annorlunda metod än i delarbete 2, där vi hade utgått från deltagarnas självrapporterade exacerbationer. I delarbete 3 använde vi i stället data om exacerbationer från patientjournaler. Vi fann att biomarkörerna CRP, fibrinogen och leukocyter var kopplade till en ökad risk för exacerbationer, medan fyra andra biomarkörer inte alls var kopplade till sådana. Återigen var kopplingarna relativt svaga, och värdet av de tre biomarkörerna kanske främst står att finna om de kombineras med andra faktorer i ett prognosverktyg.

Delarbete 4 undersökte om en enkel algoritm som utvecklats av en fransk/belgisk forskargrupp kan användas för att hitta KOL-patienter med ökad risk för exacerbationer. Återigen användes data från TIE-studien.

Algoritmen togs ursprungligen fram i syfte att hitta KOL-patienter med ökad risk för förtida död. Den använder data om fem lättillgängliga faktorer, däribland samsjuklighet, för att dela in patienterna i fem kategorier (fenotyper) med olika risk. Vi fann att algoritmen kan förutspå exacerbationer, vi bekräftade att den kan förutspå ökad risk för dödlighet och vi upptäckte dessutom att de fem fenotyperna har olika profil vad gäller inflammatoriska biomarkörer.

Sammanfattningsvis visar den här avhandlingen att samsjuklighet innebär en stark varning om att en KOL-patient har ökad risk att drabbas av förtida död, att inflammatoriska biomarkörer analyserade i blodprov kan vara till viss nytta för att förutspå KOL-exacerbationer och att en enkel algoritm kan hitta KOL-patienter med högre risk för exacerbation.

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10 References

1. Briscoe WA, Nash ES. The slow space in chronic obstructive pulmonary disease. *Ann NY Acad Sci.* 1965;121(3):706-722.
2. Petty TL. The history of COPD. *Int J Chron Obstruct Pulmon Dis.* 2006;1(1):3-14.
3. Rosenblatt MB. Emphysema in the nineteenth century. *Bull Hist Med.* 1969;43(6):533-552.
4. Laënnec RT. *De l'auscultation médiate, on traité du diagnostic des maladies des poumons et du coeur.* Brosson & Chaudé; 1819.
5. Brantigan OC, Mueller E. Surgical treatment of pulmonary emphysema. *Am Surg.* 1957;23(9):789-804.
6. Laurell C-B, Eriksson S. The Electrophoretic α 1-Globulin Pattern of Serum in α 1-Antitrypsin Deficiency. 1963. *COPD: Journal of Chronic Obstructive Pulmonary Disease.* 2013;10(sup1):3-8.
7. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J.* 1977;1(6077):1645-8.
8. Anthonisen NR. Effects of Smoking Intervention and the Use of an Inhaled Anticholinergic Bronchodilator on the Rate of Decline of FEV1. *JAMA.* 1994;272(19):1497.
9. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med.* 2005;142(4):233-9.
10. The National Lung Health Education Program (NLHEP). Strategies in Preserving Lung Health and Preventing COPD and Associated Diseases. *Chest.* 1998;113(2):123S-163S.
11. Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2001;163(5):1256-1276.
12. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease Report 2024. 2023-11-28, Updated 2023-10-30. Accessed 2023-11-28, <https://goldcopd.org/2024-gold-report/>
13. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease Report 2023. 2023-05-04, Updated 2023-02-17. Accessed 2023-05-04, <https://goldcopd.org/2023-gold-report-2/>
14. Celli B, Fabbri L, Criner G, *et al.* Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. *Am J Respir Crit Care Med.* 2022;206(11):1317-1325.
15. Backman H, Vanfleteren L, Lindberg A, *et al.* Decreased COPD prevalence in Sweden after decades of decrease in smoking. *Respir Res.* 2020;21(1):283.

16. Burney P, Patel J, Minelli C, *et al.* Prevalence and Population Attributable Risk for Chronic Airflow Obstruction in a Large Multinational Study. *Am J Respir Crit Care Med.* 2020;203(11):1353-1365.
17. Momtazmanesh S, Moghaddam SS, Ghamari S-H, *et al.* Global burden of chronic respiratory diseases and risk factors, 1990–2019: an update from the Global Burden of Disease Study 2019. *eClinicalMedicine.* 2023;59:101936.
18. Sana A, Somda SMA, Meda N, Bouland C. Chronic obstructive pulmonary disease associated with biomass fuel use in women: a systematic review and meta-analysis. *BMJ Open Respir Res.* 2018;5(1):e000246.
19. Shin S, Bai L, Burnett RT, *et al.* Air Pollution as a Risk Factor for Incident Chronic Obstructive Pulmonary Disease and Asthma. A 15-Year Population-based Cohort Study. *Am J Respir Crit Care Med.* 2021;203(9):1138-1148.
20. Rennard SI, Vestbo J. COPD: the dangerous underestimate of 15%. *Lancet.* 2006;367(9518):1216-9.
21. Cho MH, McDonald ML, Zhou X, *et al.* Risk loci for chronic obstructive pulmonary disease: a genome-wide association study and meta-analysis. *Lancet Respir Med.* 2014;2(3):214-25.
22. Varmaghani M, Dehghani M, Heidari E, Sharifi F, Moghaddam SS, Farzadfar F. Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. *East Mediterr Health J.* 2019;25(1):47-57.
23. Amaral AFS, Strachan DP, Burney PGJ, Jarvis DL. Female Smokers Are at Greater Risk of Airflow Obstruction Than Male Smokers. UK Biobank. *Am J Respir Crit Care Med.* 2017;195(9):1226-1235.
24. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet.* 2007;370(9589):758-64.
25. Lange P, Celli B, Agustí A, *et al.* Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med.* 2015;373(2):111-22.
26. Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. *Thorax.* 2005;60(10):851-8.
27. Svanes C, Sunyer J, Plana E, *et al.* Early life origins of chronic obstructive pulmonary disease. *Thorax.* 2010;65(1):14-20.
28. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined Impact of Smoking and Early-Life Exposures on Adult Lung Function Trajectories. *Am J Respir Crit Care Med.* 2017;196(8):1021-1030.
29. Fan H, Wu F, Liu J, *et al.* Pulmonary tuberculosis as a risk factor for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Ann Transl Med.* 2021;9(5):390.
30. Gelb AF, Yamamoto A, Verbeke EK, Nadel JA. Unraveling the Pathophysiology of the Asthma-COPD Overlap Syndrome. *Chest.* 2015;148(2):313-320.
31. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2016;138(1):16-27.
32. Wang Z, Locantore N, Haldar K, *et al.* Inflammatory Endotype-associated Airway Microbiome in Chronic Obstructive Pulmonary Disease Clinical Stability and Exacerbations: A Multicohort Longitudinal Analysis. *Am J Respir Crit Care Med.* 2021;203(12):1488-1502.
33. Rodrigues SO, Cunha C, Soares GMV, Silva PL, Silva AR, Goncalves-de-Albuquerque CF. Mechanisms, Pathophysiology and Currently Proposed Treatments of Chronic Obstructive Pulmonary Disease. *Pharmaceuticals (Basel).* 2021;14(10):979.

34. Hogg JC, Chu F, Utokaparch S, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(26):2645-53.
35. Rodriguez-Roisin R. The airway pathophysiology of COPD: implications for treatment. *COPD.* 2005;2(2):253-62.
36. Peinado VI, Pizarro S, Barberà JA. Pulmonary vascular involvement in COPD. *Chest.* 2008;134(4):808-814.
37. Saetta M, Turato G, Maestrelli P, Mapp CE, Fabbri LM. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;163(6):1304-9.
38. Bai S, Ye R, Wang C, Sun P, Zhao L. Comparative analysis of pathophysiological parameters between emphysematous smokers and emphysematous patients with COPD. *Sci Rep.* 2020;10(1):420.
39. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;164(5):770-7.
40. O'Donnell DE, Milne KM, James MD, De Torres JP, Neder JA. Dyspnea in COPD: New Mechanistic Insights and Management Implications. *Adv Ther.* 2020;37(1):41-60.
41. Anzueto A, Miravittles M. Pathophysiology of dyspnea in COPD. *Postgrad Med.* 2017;129(3):366-374.
42. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax.* 2004;59(7):574-80.
43. Núñez B, Sauleda J, Garcia-Aymerich J, *et al.* Lack of Correlation Between Pulmonary and Systemic Inflammation Markers in Patients with Chronic Obstructive Pulmonary Disease: A Simultaneous, Two-Compartmental Analysis. *Arch Bronconeumol.* 2016;52(7):361-367.
44. Agustí A. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). *Proc Am Thorac Soc.* 2007;4(7):522-5.
45. Kessler R, Partridge MR, Miravittles M, Cazzola M, Vogelmeier C, Leynaud D, Ostinelli J. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J.* 2011;37(2):264-72.
46. Miravittles M, Worth H, Soler Cataluna JJ, *et al.* Observational study to characterize 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. *Respir Res.* 2014;15(1):122.
47. Mahler DA, Ward J, Waterman LA, Baird JC. Longitudinal changes in patient-reported dyspnea in patients with COPD. *COPD.* 2012;9(5):522-7.
48. Goertz YMJ, Spruit MA, Van 't Hul AJ, *et al.* Fatigue is highly prevalent in patients with COPD and correlates poorly with the degree of airflow limitation. *Thorax.* 2019;13:1753466619878128.
49. Caspersen NF, Soyseth V, Lyngbakken MN, *et al.* Treatable Traits in Misdiagnosed Chronic Obstructive Pulmonary Disease: Data from the Akershus Cardiac Examination 1950 Study. *Chronic Obstr Pulm Dis.* 2022;
50. Benz E, Wijnant SRA, Trajanoska K, *et al.* Sarcopenia, systemic immune-inflammation index and all-cause mortality in middle-aged and older people with COPD and asthma: a population-based study. *ERJ Open Res.* 2022;8(1):00628-2021.
51. Collins PF, Yang IA, Chang YC, Vaughan A. Nutritional support in chronic obstructive pulmonary disease (COPD): an evidence update. *J Thorac Dis.* 2019;11(Suppl 17):S2230-S2237.

52. Miller J, Edwards LD, Agusti A, *et al.* Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir Med.* 2013;107(9):1376-84.
53. Pumar MI, Gray CR, Walsh JR, Yang IA, Rolls TA, Ward DL. Anxiety and depression—Important psychological comorbidities of COPD. *J Thorac Dis.* 2014;6(11):1615-1631.
54. Behandlingsrekommendation: Kroniskt obstruktiv lungsjukdom (KOL) (Läke-medelsverket) (2023).
55. Wollmer P, Engström G. Fixed ratio or lower limit of normal as cut-off value for FEV1/VC: An outcome study. *Respir Med.* 2013;107(9):1460-1462.
56. O'Donnell DE. Breathlessness in patients with chronic airflow limitation. Mechanisms and management. *Chest.* 1994;106(3):904-12.
57. Torén K, Olin AC, Lindberg A, *et al.* Vital capacity and COPD: the Swedish CARDioPulmonary bioImage Study (SCAPIS). *Int J Chron Obstruct Pulmon Dis.* 2016;11:927-33.
58. Hurst JR, Han MK, Singh B, *et al.* Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease: a systematic literature review. *Respir Res.* 2022;23(1):213.
59. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1986;133(1):14-20.
60. Jones PW, Harding G, Berry P, Wiklund I, Chen W-H, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J.* 2009;34(3):648-654.
61. Mahler DA, Rosiello RA, Harver A, Lentine T, McGovern JF, Daubenspeck JA. Comparison of clinical dyspnea ratings and psychophysical measurements of respiratory sensation in obstructive airway disease. *Am Rev Respir Dis.* 1987;135(6):1229-33.
62. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest.* 2005;128(4):2099-107.
63. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J.* 2008;32(4):962-9.
64. Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax.* 2010;65(11):956-62.
65. Schnell K, Weiss CO, Lee T, Krishnan JA, Leff B, Wolff JL, Boyd C. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999-2008. *BMC Pulm Med.* 2012;12:26.
66. Ställberg B, Janson C, Larsson K, *et al.* Real-world retrospective cohort study ARCTIC shows burden of comorbidities in Swedish COPD versus non-COPD patients. *NPJ Prim Care Respir Med.* 2018;28(1):33.
67. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. *Transl Res.* 2013;162(4):237-51.
68. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J.* 2009;33(5):1165-85.
69. Putcha N, Han MK, Martinez CH, *et al.* Comorbidities of COPD have a major impact on clinical outcomes, particularly in African Americans. *Chronic Obstr Pulm Dis.* 2014;1(1):105-114.

70. Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1465-75.
71. Ingebrigtsen TS, Marott JL, Vestbo J, Nordestgaard BG, Hallas J, Lange P. Gastro-esophageal reflux disease and exacerbations in chronic obstructive pulmonary disease. *Respirology.* 2015;20(1):101-7.
72. Axson EL, Bottle A, Cowie MR, Quint JK. Relationship between heart failure and the risk of acute exacerbation of COPD. *Thorax.* 2021;76(8):807-814.
73. Divo M, Cote C, de Torres JP, *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012;186(2):155-61.
74. Baty F, Putora PM, Isenring B, Blum T, Brutsche M. Comorbidities and burden of COPD: a population based case-control study. *PLoS One.* 2013;8(5):e63285.
75. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. *Eur Respir J.* 2006;28(6):1245-57.
76. Axson EL, Ragutheeswaran K, Sundaram V, Bloom CI, Bottle A, Cowie MR, Quint JK. Hospitalisation and mortality in patients with comorbid COPD and heart failure: a systematic review and meta-analysis. *Respir Res.* 2020;21(1):54.
77. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-83.
78. Figueira-Gonçalves JM, Golpe R, García-Bello MÁ, García-Talavera I, Castro-Añón O. Comparison of the prognostic capability of two comorbidity indices in patients with chronic obstructive pulmonary disease, in real-life clinical practice. *Clin Resp J.* 2019;13(6):404-407.
79. Lisspers K, Larsson K, Johansson G, *et al.* Economic burden of COPD in a Swedish cohort: the ARCTIC study. *Int J Chron Obstruct Pulmon Dis.* 2018;13:275-285.
80. Cosio BG, Soriano JB, López-Campos JL, *et al.* Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort. *Chest.* 2016;149(1):45-52.
81. Sorino C, Pedone C, Scichilone N. Fifteen-year mortality of patients with asthma-COPD overlap syndrome. *Eur J Intern Med.* 2016;34:72-77.
82. Gayle AV, Minelli C, Quint JK. Respiratory-related death in individuals with incident asthma and COPD: a competing risk analysis. *BMC Pulm Med.* 2022;22(1):28.
83. Lange P, Colak Y, Ingebrigtsen TS, Vestbo J, Marott JL. Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. *Lancet Respir Med.* 2016;4(6):454-62.
84. Diaz-Guzman E, Khosravi M, Mannino DM. Asthma, Chronic Obstructive Pulmonary Disease, and Mortality in the U.S. Population. *COPD.* 2011;8(6):400-407.
85. Bateman ED, Reddel HK, van Zyl-Smit RN, Agusti A. The asthma-COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? *Lancet Respir Med.* 2015;3(9):719-728.
86. Celli BR, Fabbri LM, Aaron SD, *et al.* An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *Am J Respir Crit Care Med.* 2021;204(11):1251-1258.

87. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med.* 1987;106(2):196-204.
88. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest.* 2000;117(5 Suppl 2):398S-401S.
89. Pauwels R, Calverley P, Buist AS, Rennard S, Fukuchi Y, Stahl E, Löfdahl CG. COPD exacerbations: the importance of a standard definition. *Respir Med.* 2004;98(2):99-107.
90. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J.* 2007;29(6):1224-38.
91. Wedzicha JA, Calverley PMA, Albert RK, *et al.* Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2017;50(3):1602265.
92. Kim V, Aaron SD. What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement. *Eur Respir J.* 2018;52(5)
93. Miravittles M, Ferrer M, Pont À, *et al.* Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax.* 2004;59(5):387-95.
94. Dransfield MT, Kunisaki KM, Strand MJ, *et al.* Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2017;195(3):324-330.
95. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest.* 2010;137(5):1091-7.
96. Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, Garau J. Mortality after hospitalization for COPD. *Chest.* 2002;121(5):1441-8.
97. Soler-Cataluña JJ, Martínez-García MÁ, Roman Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax.* 2005;60(11):925-31.
98. Anzueto A, Leimer I, Kesten S. Impact of frequency of COPD exacerbations on pulmonary function, health status and clinical outcomes. *Int J Chron Obstruct Pulmon Dis.* 2009;4:245-51.
99. Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. Article. *N Engl J Med.* 2010;363(12):1128-38.
100. O'Donnell DE, Parker CM. COPD exacerbations 3: Pathophysiology. *Thorax.* 2006;61(4):354-61.
101. Barberà JA, Roca J, Ferrer A, Félez MA, Díaz O, Roger N, Rodriguez-Roisin R. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. *Eur Respir J.* 1997;10(6):1285-91.
102. Bafadhel M, McKenna S, Terry S, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med.* 2011;184(6):662-71.
103. Ghebre MA, Pang PH, Diver S, *et al.* Biological exacerbation clusters demonstrate asthma and chronic obstructive pulmonary disease overlap with distinct mediator and microbiome profiles. *J Allergy Clin Immunol.* 2018;141(6):2027-2036 e12.
104. Bouhuis D, Giezeman M, Hasselgren M, *et al.* Factors Associated with the Non-Exacerbator Phenotype of Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis.* 2023;18:483-492.

105. Le Rouzic O, Roche N, Cortot AB, *et al.* Defining the "Frequent Exacerbator" Phenotype in COPD: A Hypothesis-Free Approach. *Chest.* 2018;153(5):1106-1115.
106. Li J, Sun S, Tang R, Qiu H, Huang Q, Mason TG, Tian L. Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2016;11:3079-3091.
107. Miravittles M, Guerrero T, Mayordomo C, Sánchez-Agudo L, Nicolau F, Segú JL. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. *Respiration.* 2000;67(5):495-501.
108. Fermont JM, Masconi KL, Jensen MT, *et al.* Biomarkers and clinical outcomes in COPD: a systematic review and meta-analysis. *Thorax.* 2019;74(5):439-446.
109. Donaldson GC, Wedzicha JA. COPD exacerbations 1: Epidemiology. *Thorax.* 2006;61(2):164-8.
110. Aaron SD, Donaldson GC, Whitmore GA, Hurst JR, Ramsay T, Wedzicha JA. Time course and pattern of COPD exacerbation onset. *Thorax.* 2012;67(3):238-43.
111. Ställberg B, Janson C, Johansson G, Larsson K, Stratelis G, Telg G, Lisspers KH. Management, morbidity and mortality of COPD during an 11-year period: an observational retrospective epidemiological register study in Sweden (PATHOS). *Prim Care Respir J.* 2014;23(1):38-45.
112. Casanova C, Cote C, Marin JM, *et al.* Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD. *Chest.* 2008;134(4):746-52.
113. Gray-Donald K, Gibbons L, Shapiro SH, Macklem PT, Martin JG. Nutritional status and mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1996;153(3):961-6.
114. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest.* 2002;121(5):1434-40.
115. Gershon AS, Dolmage TE, Stephenson A, Jackson B. Chronic obstructive pulmonary disease and socioeconomic status: a systematic review. *COPD.* 2012;9(3):216-26.
116. Xiong W, Xu M, Zhao Y, Wu X, Pudasaini B, Liu JM. Can we predict the prognosis of COPD with a routine blood test? *Int J Chron Obstruct Pulmon Dis.* 2017;12:615-625.
117. Larsson K, Janson C, Lisspers K, *et al.* The Impact of Exacerbation Frequency on Clinical and Economic Outcomes in Swedish COPD Patients: The ARCTIC Study. *Int J Chron Obstruct Pulmon Dis.* 2021;16:701-713.
118. Rysø CK, Godtfredsen NS, Kofod LM, *et al.* Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis. *BMC Pulm Med.* 2018;18(1):154.
119. Fishman A, Martinez F, Naunheim K, *et al.* A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med.* 2003;348(21):2059-73.
120. Murphy PB, Rehal S, Arbane G, *et al.* Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. *JAMA.* 2017;317(21):2177-2186.

121. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med.* 1980;93(3):391-8.
122. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet.* 1981;1(8222):681-6.
123. Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP, Investigators US. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2009;180(10):948-55.
124. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2014;7:CD009285.
125. Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2013;11:CD003794.
126. Vestbo J, Anderson JA, Brook RD, *et al.* Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet.* 2016;387(10030):1817-26.
127. Lipson DA, Crim C, Criner GJ, *et al.* Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2020;201(12):1508-1516.
128. Martinez FJ, Rabe KF, Ferguson GT, *et al.* Reduced All-Cause Mortality in the ETHOS Trial of Budesonide/Glycopyrrolate/Formoterol for Chronic Obstructive Pulmonary Disease. A Randomized, Double-Blind, Multicenter, Parallel-Group Study. *Am J Respir Crit Care Med.* 2021;203(5):553-564.
129. Chen H, Deng Z-X, Sun J, *et al.* Association of Inhaled Corticosteroids With All-Cause Mortality Risk in Patients With COPD: A Meta-analysis of 60 Randomized Controlled Trials. *Chest.* 2023;163(1):100-114.
130. Suissa S, Dell'Aniello S, Ernst P. Triple Inhaler versus Dual Bronchodilator Therapy in COPD: Real-World Effectiveness on Mortality. *COPD.* 2021;1-9.
131. Horita N, Miyazawa N, Kojima R, Inoue M, Ishigatsubo Y, Ueda A, Kaneko T. Statins reduce all-cause mortality in chronic obstructive pulmonary disease: a systematic review and meta-analysis of observational studies. *Respir Res.* 2014;15:80.
132. Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol.* 2006;47(12):2554-60.
133. Mortensen EM, Copeland LA, Pugh MJ, Restrepo MI, de Molina RM, Nakashima B, Anzueto A. Impact of statins and ACE inhibitors on mortality after COPD exacerbations. *Respir Res.* 2009;10:45.
134. Ho TW, Tsai YJ, Ruan SY, Huang CT, Lai F, Yu CJ, Group HS. In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. *PLoS One.* 2014;9(12):e114866.
135. Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. *PLoS One.* 2014;9(11):e113048.

136. Ekström MP, Hermansson AB, Ström KE. Effects of cardiovascular drugs on mortality in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(7):715-20.
137. Qian J, Simoni-Wastila L, Langenberg P, Rattinger GB, Zuckerman IH, Lehmann S, Terrin M. Effects of depression diagnosis and antidepressant treatment on mortality in Medicare beneficiaries with chronic obstructive pulmonary disease. *J Am Geriatr Soc*. 2013;61(5):754-61.
138. Bakshi A, Suissa S. Effectiveness of Aspirin in COPD: Biases in the Observational Studies. *COPD*. 2021;18(4):449-455.
139. Suissa S, Ernst P. Beta-Blockers in COPD: A Methodological Review of the Observational Studies. *COPD*. 2018;15(5):520-525.
140. Suissa S. Co-morbidity in COPD: the effects of cardiovascular drug therapies. *Respiration*. 2010;80(1):3-7.
141. Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med*. 2014;370(23):2201-10.
142. Dransfield MT, Voelker H, Bhatt SP, et al. Metoprolol for the Prevention of Acute Exacerbations of COPD. *N Engl J Med*. 2019;381(24):2304-2314.
143. Guerra B, Haile SR, Lamprecht B, et al. Large-scale external validation and comparison of prognostic models: an application to chronic obstructive pulmonary disease. *BMC Med*. 2018;16(1):33.
144. Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *The Lancet*. 2009;374(9691):704-711.
145. Puhan MA, Hansel NN, Sobradillo P, et al. Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts. *BMJ Open*. 2012;2(6):e002152.
146. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005-12.
147. Soler-Cataluña JJ, Martínez-García MÁ, Sánchez LS, Tordera MP, Sánchez PR. Severe exacerbations and BODE index: Two independent risk factors for death in male COPD patients. *Respir Med*. 2009;103(5):692-699.
148. Jones RC, Donaldson GC, Chavannes NH, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. *Am J Respir Crit Care Med*. 2009;180(12):1189-95.
149. Burgel PR, Paillasseur JL, Janssens W, et al. A simple algorithm for the identification of clinical COPD phenotypes. *Eur Respir J*. 2017;50(5):1701034.
150. Guo Y, Zhang T, Wang Z, et al. Body mass index and mortality in chronic obstructive pulmonary disease: A dose-response meta-analysis. *Medicine*. 2016;95(28):e4225.
151. Gagatek S, Wijnant SRA, Ställberg B, et al. Validation of Clinical COPD Phenotypes for Prognosis of Long-Term Mortality in Swedish and Dutch Cohorts. *COPD*. 2022;19(1):330-338.
152. Koblizek V, Milenkovic B, Svoboda M, et al. RETRO-POPE: A Retrospective, Multicenter, Real-World Study of All-Cause Mortality in COPD. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2661-2672.
153. Guerra B, Gaveikaite V, Bianchi C, Puhan MA. Prediction models for exacerbations in patients with COPD. *Eur Respir Rev*. 2017;26(143):160061.
154. Ho JK, Safari A, Adibi A, et al. Generalizability of Risk Stratification Algorithms for Exacerbations in COPD. *Chest*. 2023;163(4):790-798.

155. Adibi A, Sin DD, Safari A, Johnson KM, Aaron SD, FitzGerald JM, Sadatsafavi M. The Acute COPD Exacerbation Prediction Tool (ACCEPT): a modeling study. *Lancet Respir Med.* 2020;8(10):1013-1021.
156. Vanfleteren LE, Kocks JW, Stone IS, *et al.* Moving from the Oslerian paradigm to the post-genomic era: are asthma and COPD outdated terms? *Thorax.* 2014;69(1):72-9.
157. Han MK, Agustí A, Calverley PM, *et al.* Chronic Obstructive Pulmonary Disease Phenotypes. *Am J Respir Crit Care Med.* 2010;182(5):598-604.
158. Woodruff PG, Agustí A, Roche N, Singh D, Martinez FJ. Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy: making progress towards personalised management. *Lancet.* 2015;385(9979):1789-1798.
159. Lötvall J, Akdis CA, Bacharier LB, *et al.* Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol.* 2011;127(2):355-360.
160. Barnes PJ. Inflammatory endotypes in COPD. *Allergy.* 2019;74(7):1249-1256.
161. Russell DW, Wells JM, Blalock JE. Disease phenotyping in chronic obstructive pulmonary disease: the neutrophilic endotype. *Curr Opin Pulm Med.* 2016;22(2):91-9.
162. Li A, Chan HP, Gan PXL, Liew MF, Wong WSF, Lim HF. Eosinophilic endotype of chronic obstructive pulmonary disease: similarities and differences from asthma. *Korean J Intern Med.* 2021;36(6):1305-1319.
163. Agustí A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J.* 2016;47(2):410-9.
164. McDonald VM, Fingleton J, Agustí A, *et al.* Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *Eur Respir J.* 2019;53(5):1802058.
165. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Food and Drug Administration (US); National Institutes of Health (US). Updated 2021-11-29. Accessed 2024-02-10, <https://www.ncbi.nlm.nih.gov/books/NBK326791/>
166. de Vet HC, Terwee CB, Knol DL, Bouter LM. When to use agreement versus reliability measures. *J Clin Epidemiol.* 2006;59(10):1033-9.
167. Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic Obstructive Pulmonary Disease Biomarkers and Their Interpretation. *Am J Respir Crit Care Med.* 2019;199(10):1195-1204.
168. Agustí A, Edwards LD, Rennard SI, *et al.* Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One.* 2012;7(5):e37483.
169. Keene JD, Jacobson S, Kechris K, *et al.* Biomarkers Predictive of Exacerbations in the SPIROMICS and COPD Gene Cohorts. *Am J Respir Crit Care Med.* 2017;195(4):473-481.
170. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest.* 2003;111(12):1805-1812.
171. Leuzzi G, Galeone C, Taverna F, Suatoni P, Morelli D, Pastorino U. C-reactive protein level predicts mortality in COPD: a systematic review and meta-analysis. *European Respiratory Review.* 2017;26(143):160070.
172. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation.* 2003;107(11):1514-9.

173. Hurst JR, Donaldson GC, Perera WR, *et al.* Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2006;174(8):867-74.
174. Hoult G, Gillespie D, Wilkinson TMA, Thomas M, Francis NA. Biomarkers to guide the use of antibiotics for acute exacerbations of COPD (AECOPD): a systematic review and meta-analysis. *BMC Pulm Med.* 2022;22(1):194.
175. Husebø GR, Bakke PS, Aanerud M, *et al.* Predictors of exacerbations in chronic obstructive pulmonary disease - results from the Bergen COPD cohort study. *PLoS One.* 2014;9(10):e109721.
176. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjærg-Hansen A, Nordestgaard BG. C-reactive Protein As a Predictor of Prognosis in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2007;175(3):250-255.
177. Dahl M, Vestbo J, Zacho J, Lange P, Tybjærg-Hansen A, Nordestgaard BG. C reactive protein and chronic obstructive pulmonary disease: a Mendelian randomisation approach. *Thorax.* 2011;66(3):197-204.
178. Celli BR, Anderson JA, Brook R, *et al.* Serum biomarkers and outcomes in patients with moderate COPD: a substudy of the randomised SUMMIT trial. *BMJ Open Respir Res.* 2019;6(1):e000431.
179. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *JAMA.* 2013;309(22):2353-61.
180. Lowe GD, Rumley A, Mackie IJ. Plasma fibrinogen. *Ann Clin Biochem.* 2004;41(6):430-440.
181. Mannino DM, Tal-Singer R, Lomas DA, *et al.* Plasma Fibrinogen as a Biomarker for Mortality and Hospitalized Exacerbations in People with COPD. *Chronic Obstr Pulm Dis.* 2015;2(1):23-34.
182. Groenewegen KH, Postma DS, Hop WC, Wielders PL, Schlosser NJ, Wouters EF, Group CS. Increased systemic inflammation is a risk factor for COPD exacerbations. *Chest.* 2008;133(2):350-7.
183. Kim TH, Oh DK, Oh Y-M, Lee SW, Lee SD, Lee JS. Fibrinogen as a potential biomarker for clinical phenotype in patients with chronic obstructive pulmonary disease. *J Thorac Dis.* 2018;10(9):5260-5268.
184. Singh D, Criner GJ, Dransfield MT, *et al.* InforMing the PATHway of COPD Treatment (IMPACT) trial: fibrinogen levels predict risk of moderate or severe exacerbations. *Respir Res.* 2021;22(1):130.
185. Müllerova H, Maselli DJ, Locantore N, *et al.* Hospitalized Exacerbations of COPD: Risk Factors and Outcomes in the ECLIPSE Cohort. *Chest.* 2015;147(4):999-1007.
186. Engström G, Segelstorm N, Ekberg-Aronsson M, Nilsson PM, Lindgärde F, Löfdahl C-G. Plasma markers of inflammation and incidence of hospitalisations for COPD: results from a population-based cohort study. *Thorax.* 2009;64(3):211-215.
187. Miller BE, Tal-Singer R, Rennard SI, *et al.* Plasma Fibrinogen Qualification as a Drug Development Tool in Chronic Obstructive Pulmonary Disease. Perspective of the Chronic Obstructive Pulmonary Disease Biomarker Qualification Consortium. *Am J Respir Crit Care Med.* 2016;193(6):607-613.
188. Mallah H, Ball S, Sekhon J, Parmar K, Nugent K. Platelets in chronic obstructive pulmonary disease: An update on pathophysiology and implications for antiplatelet therapy. *Respir Med.* 2020;171:106098.
189. Manne BK, Xiang SC, Rondina MT. Platelet secretion in inflammatory and infectious diseases. *Platelets.* 2017;28(2):155-164.

190. Zinellu A, Paliogiannis P, Sotgiu E, Mellino S, Fois AG, Carru C, Mangoni AA. Platelet Count and Platelet Indices in Patients with Stable and Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *COPD*. 2021;18(2):231-245.
191. Maclay JD, McAllister DA, Johnston S, *et al*. Increased platelet activation in patients with stable and acute exacerbation of COPD. *Thorax*. 2011;66(9):769-74.
192. Kunadian V, Wilson N, Stocken DD, *et al*. Antiplatelet therapy in the primary prevention of cardiovascular disease in patients with chronic obstructive pulmonary disease: a randomised controlled proof-of-concept trial. *ERJ Open Res*. 2019;5(3):00110-2019.
193. Yoon EC, Koo S-M, Park HY, *et al*. Predictive Role of White Blood Cell Differential Count for the Development of Acute Exacerbation in Korean Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis*. 2024;Volume 19:17-31.
194. Butler A, Walton GM, Sapey E. Neutrophilic Inflammation in the Pathogenesis of Chronic Obstructive Pulmonary Disease. *COPD*. 2018;15(4):392-404.
195. Hartjes FJ, Vonk JM, Faiz A, *et al*. Predictive value of eosinophils and neutrophils on clinical effects of ICS in COPD. *Respirology*. 2018;23(11):1023-1031.
196. Kang HS, Rhee CK, Kim SK, *et al*. Comparison of the clinical characteristics and treatment outcomes of patients requiring hospital admission to treat eosinophilic and neutrophilic exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2467-2473.
197. Pascoe SJ, Papi A, Midwinter D, Lettis S, Barnes N. Circulating neutrophils levels are a predictor of pneumonia risk in chronic obstructive pulmonary disease. *Respir Res*. 2019;20(1):195.
198. Lonergan M, Dicker AJ, Crichton ML, *et al*. Blood neutrophil counts are associated with exacerbation frequency and mortality in COPD. *Respir Res*. 2020;21(1):166.
199. de Jong JW, van der Belt-Gritter B, Koeter GH, Postma DS. Peripheral blood lymphocyte cell subsets in subjects with chronic obstructive pulmonary disease: association with smoking, IgE and lung function. *Respir Med*. 1997;91(2):67-76.
200. Semenzato U, Biondini D, Bazzan E, *et al*. Low-Blood Lymphocyte Number and Lymphocyte Decline as Key Factors in COPD Outcomes: A Longitudinal Cohort Study. *Respiration*. 2021;100(7):618-630.
201. Halper-Stromberg E, Yun JH, Parker MM, *et al*. Systemic Markers of Adaptive and Innate Immunity Are Associated with Chronic Obstructive Pulmonary Disease Severity and Spirometric Disease Progression. *Am J Respir Cell Mol Biol*. 2018;58(4):500-509.
202. Moon SW, Leem AY, Kim YS, *et al*. Low serum lymphocyte level is associated with poor exercise capacity and quality of life in chronic obstructive pulmonary disease. *Sci Rep*. 2020;10(1):11700.
203. Warny M, Helby J, Nordestgaard BG, Birgens H, Bojesen SE. Incidental lymphopenia and mortality: a prospective cohort study. *Can Med Assoc J*. 2020;192(2):E25-E33.
204. David B, Bafadhel M, Koenderman L, De Soyza A. Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait. *Thorax*. 2021;76(2):188-195.
205. Saha S, Brightling CE. Eosinophilic airway inflammation in COPD. *Int J Chron Obstruct Pulmon Dis*. 2006;1(1):39-47.

206. Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? *Lancet Respir Med.* 2017;5(9):747-759.
207. Kolsum U, Damera G, Pham TH, *et al.* Pulmonary inflammation in patients with chronic obstructive pulmonary disease with higher blood eosinophil counts. *J Allergy Clin Immunol.* 2017;140(4):1181-1184 e7.
208. Negewo NA, McDonald VM, Baines KJ, Wark PA, Simpson JL, Jones PW, Gibson PG. Peripheral blood eosinophils: a surrogate marker for airway eosinophilia in stable COPD. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1495-504.
209. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med.* 2016;193(9):965-74.
210. Yun JH, Lamb A, Chase R, *et al.* Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2018;141(6):2037-2047 e10.
211. Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, Fagerås M. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med.* 2018;6(2):117-126.
212. Pascoe S, Pavord I, Hinds D, Locantore N, Barnes N. The association between blood eosinophils and risk and treatment outcome in COPD is not dichotomised. *Lancet Respir Med.* 2018;6(5):e18.
213. Pascoe S, Barnes N, Brusselle G, *et al.* Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. *Lancet Respir Med.* 2019;7(9):745-756.
214. Zeiger RS, Tran TN, Butler RK, *et al.* Relationship of Blood Eosinophil Count to Exacerbations in Chronic Obstructive Pulmonary Disease. *J Allergy Clin Immunol Pract.* 2018;6(3):944-954.e5.
215. Müllerová H, Hahn B, Simard EP, Mu G, Hatipoğlu U. Exacerbations and health care resource use among patients with COPD in relation to blood eosinophil counts. *Int J Chron Obstruct Pulmon Dis.* 2019;Volume 14:683-692.
216. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J.* 2014;44(6):1697-700.
217. Casanova C, Celli BR, de-Torres JP, *et al.* Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. *Eur Respir J.* 2017;50(5):1701162.
218. Zysman M, Deslee G, Caillaud D, *et al.* Relationship between blood eosinophils, clinical characteristics, and mortality in patients with COPD. *Int J Chron Obstruct Pulmon Dis.* 2017;12:1819-1824.
219. Adir Y, Hakrush O, Shteinberg M, Schneer S, Agusti A. Circulating eosinophil levels do not predict severe exacerbations in COPD: a retrospective study. *ERJ Open Res.* 2018;4(3):00022-2018.
220. Singh D, Wedzicha JA, Siddiqui S, *et al.* Blood eosinophils as a biomarker of future COPD exacerbation risk: pooled data from 11 clinical trials. *Respir Res.* 2020;21(1):240.
221. Miravittles M, Monteagudo M, Solntseva I, Alcázar B. Blood Eosinophil Counts and Their Variability and Risk of Exacerbations in COPD: A Population-Based Study. *Arch Bronconeumol.* 2021;57(1):13-20.

222. Turato G, Semenzato U, Bazzan E, *et al.* Blood Eosinophilia Neither Reflects Tissue Eosinophils nor Worsens Clinical Outcomes in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2018;197(9):1216-1219.
223. Shin SH, Park HY, Kang D, *et al.* Serial blood eosinophils and clinical outcome in patients with chronic obstructive pulmonary disease. *Respir Res.* 2018;19(1):134.
224. Han MK, Quibrera PM, Carretta EE, *et al.* Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med.* 2017;5(8):619-626.
225. Hoppers JJ, Schouten JP, Weiss ST, Rijcken B, Postma DS. Asthma attacks with eosinophilia predict mortality from chronic obstructive pulmonary disease in a general population sample. *Am J Respir Crit Care Med.* 1999;160(6):1869-74.
226. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax.* 2012;67(11):970-6.
227. Oh YM, Lee KS, Hong Y, *et al.* Blood eosinophil count as a prognostic biomarker in COPD. Article. *Int J Chron Obstruct Pulmon Dis.* 2018;13:3589-3596.
228. Miravittles M, Soler-Cataluña JJ, Soriano JB, *et al.* Determinants of blood eosinophil levels in the general population and patients with COPD: a population-based, epidemiological study. *Respir Res.* 2022;23(1):49.
229. Caspard H, Ambrose CS, Tran TN, Chipps BE, Zeiger RS. Associations Between Individual Characteristics and Blood Eosinophil Counts in Adults with Asthma or COPD. *J Allergy Clin Immunol Pract.* 2020;8(5):1606-1613 e1.
230. Song JH, Lee CH, Kim JW, *et al.* Clinical implications of blood eosinophil count in patients with non-asthma-COPD overlap syndrome COPD. *Int J Chron Obstruct Pulmon Dis.* 2017;12:2455-2464.
231. Kerkhof M, Sonnappa S, Postma DS, *et al.* Blood eosinophil count and exacerbation risk in patients with COPD. *Eur Respir J.* 2017;50(1):1700761.
232. Mathioudakis AG, Bikov A, Foden P, Lahousse L, Brusselle G, Singh D, Vestbo J. Change in blood eosinophils following treatment with inhaled corticosteroids may predict long-term clinical response in COPD. *Eur Respir J.* 2020;55(5):1902119.
233. Ortega H, Llanos J-P, Lafeuille M-H, *et al.* Effects of systemic corticosteroids on blood eosinophil counts in asthma: real-world data. *J Asthma.* 2019;56(8):808-815.
234. Van Rossem I, Hanon S, Verbanck S, Vanderhelst E. Blood Eosinophil Counts in Chronic Obstructive Pulmonary Disease: Adding Within-Day Variability to the Equation. *Am J Respir Crit Care Med.* 2022;205(6):727-729.
235. Landis S, Suruki R, Maskell J, Bonar K, Hilton E, Compton C. Demographic and Clinical Characteristics of COPD Patients at Different Blood Eosinophil Levels in the UK Clinical Practice Research Datalink. *COPD.* 2018;15(2):177-184.
236. Southworth T, Beech G, Foden P, Kolsum U, Singh D. The reproducibility of COPD blood eosinophil counts. *Eur Respir J.* 2018;52(1):1800427.
237. Martínez-Gestoso S, García-Sanz M-T, Calvo-Álvarez U, *et al.* Variability of blood eosinophil count and prognosis of COPD exacerbations. *Ann Med.* 2021;53(1):1152-1158.
238. Landis SH, Suruki R, Hilton E, Compton C, Galwey NW. Stability of Blood Eosinophil Count in Patients with COPD in the UK Clinical Practice Research Datalink. *COPD.* 2017;14(4):382-388.

239. Long GH, Southworth T, Kolsum U, Donaldson GC, Wedzicha JA, Brightling CE, Singh D. The stability of blood Eosinophils in chronic obstructive pulmonary disease. *Respir Res.* 2020;21(1):15.
240. Referensintervall för differentialräkning av leukocyt-koncentrationer i blod (S024). EQUALIS. Updated 2020-01-10. Accessed 2024-02-18, https://www.equalis.se/media/4jnnhio1/s024_referensintervall-f%C3%B6r-differentialr%C3%A4kning-av-leukocyt-koncentrationer-i-blod_1-1.pdf
241. Harries TH, Rowland V, Corrigan CJ, *et al.* Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: systematic review and meta-analysis. *Respir Res.* 2020;21(1):3.
242. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *Lancet Respir Med.* 2018;6(11):855-862.
243. Kapellos TS, Bonaguro L, Gemünd I, Reusch N, Saglam A, Hinkley ER, Schultze JL. Human Monocyte Subsets and Phenotypes in Major Chronic Inflammatory Diseases. Review. *Front Immunol.* 2019;10:2035.
244. Cornwell WD, Kim V, Fan X, Vega ME, Ramsey FV, Criner GJ, Rogers TJ. Activation and polarization of circulating monocytes in severe chronic obstructive pulmonary disease. *BMC Pulm Med.* 2018;18(1):101.
245. Lin CH, Li YR, Lin PR, Wang BY, Lin SH, Huang KY, Kor CT. Blood monocyte levels predict the risk of acute exacerbations of chronic obstructive pulmonary disease: a retrospective case-control study. *Sci Rep.* 2022;12(1):21057.
246. Song M, Graubard BI, Rabkin CS, Engels EA. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. *Sci Rep.* 2021;11(1):464.
247. Gao X, Coull B, Lin X, *et al.* Association of Neutrophil to Lymphocyte Ratio With Pulmonary Function in a 30-Year Longitudinal Study of US Veterans. *JAMA Netw Open.* 2020;3(7):e2010350.
248. Pascual-González Y, López-Sánchez M, Dorca J, Santos S. Defining the role of neutrophil-to-lymphocyte ratio in COPD: a systematic literature review. *Int J Chron Obstruct Pulmon Dis.* 2018;13:3651-3662.
249. Paliogiannis P, Fois AG, Sotgia S, *et al.* The neutrophil-to-lymphocyte ratio as a marker of chronic obstructive pulmonary disease and its exacerbations: A systematic review and meta-analysis. *Eur J Clin Invest.* 2018;48(8):e12984.
250. Guo R, Li J, Ma X, Pan L. The predictive value of neutrophil-to-lymphocyte ratio for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Expert Rev Respir Med.* 2020;14(9):929-936.
251. Duman D, Aksoy E, Agca MC, *et al.* The utility of inflammatory markers to predict readmissions and mortality in COPD cases with or without eosinophilia. *Int J Chron Obstruct Pulmon Dis.* 2015;10:2469-78.
252. Yao C, Liu X, Tang Z. Prognostic role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio for hospital mortality in patients with AECOPD. *Int J Chron Obstruct Pulmon Dis.* 2017;12:2285-2290.
253. Sørensen AK, Holmgaard DB, Mygind LH, Johansen J, Pedersen C. Neutrophil-to-lymphocyte ratio, calprotectin and YKL-40 in patients with chronic obstructive pulmonary disease: correlations and 5-year mortality - a cohort study. *J Inflamm (Lond).* 2015;12:20.
254. Lee H, Um SJ, Kim YS, *et al.* Association of the Neutrophil-to-Lymphocyte Ratio with Lung Function and Exacerbations in Patients with Chronic Obstructive Pulmonary Disease. *PLoS One.* 2016;11(6):e0156511.

255. Lee SJ, Lee HR, Lee TW, *et al.* Usefulness of neutrophil to lymphocyte ratio in patients with chronic obstructive pulmonary disease: a prospective observational study. *Korean J Intern Med.* 2016;31(5):891-8.
256. Sakurai K, Chubachi S, Irie H, *et al.* Clinical utility of blood neutrophil-lymphocyte ratio in Japanese COPD patients. *BMC Pulm Med.* 2018;18(1):65.
257. Mendy A, Forno E, Niyonsenga T, Gasana J. Blood biomarkers as predictors of long-term mortality in COPD. *Clin Respir J.* 2018;12(5):1891-1899.
258. Liu X, Ge H, Feng X, *et al.* The Combination of Hemogram Indexes to Predict Exacerbation in Stable Chronic Obstructive Pulmonary Disease. Original Research. *Front Med (Lausanne).* 2020;7
259. Hosseninia S, Ghobadi H, Garjani K, Hosseini SAH, Aslani MR. Aggregate index of systemic inflammation (AISI) in admission as a reliable predictor of mortality in COPD patients with COVID-19. *BMC Pulm Med.* 2023;23(1):107.
260. Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319-338.
261. Hedenström H, Malmberg P, Agarwal K. Reference values for lung function tests in females. Regression equations with smoking variables. *Bull Eur Physiopathol Respir.* 1985;21(6):551-7.
262. Hedenström H, Malmberg P, Fridriksson HV. Reference values for lung function tests in men: regression equations with smoking variables. *Ups J Med Sci.* 1986;91(3):299-310.
263. Quan H, Sundararajan V, Halfon P, *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130-9.
264. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med.* 2016;15(2):155-163.
265. Bao W, Li Y, Wang T, *et al.* Effects of influenza vaccination on clinical outcomes of chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Ageing Res Rev.* 2021;68:101337.
266. Fedeli U, Casotto V, Barbiellini Amidei C, Vianello A, Guarnieri G. COPD-Related Mortality before and after Mass COVID-19 Vaccination in Northern Italy. *Vaccines.* 2023;11(8):1392.
267. Danaei G, Tavakkoli M, Hernán MA. Bias in Observational Studies of Prevalent Users: Lessons for Comparative Effectiveness Research From a Meta-Analysis of Statins. *Am J Epidemiol.* 2012;175(4):250-262.
268. Sethi S, Evans N, Grant BJB, Murphy TF. New Strains of Bacteria and Exacerbations of Chronic Obstructive Pulmonary Disease. *N Engl J Med.* 2002;347(7):465-471.
269. Jenkins CR, Celli B, Anderson JA, *et al.* Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur Respir J.* 2012;39(1):38-45.
270. Sidney S, Sorel M, Quesenberry CP, Jr., DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest.* 2005;128(4):2068-75.
271. Kaszuba E, Odeberg H, Råstam L, Halling A. Impact of heart failure and other comorbidities on mortality in patients with chronic obstructive pulmonary disease: a register-based, prospective cohort study. *BMC Fam Pract.* 2018;19(1):178.
272. Antonelli Incalzi R, Fuso L, De Rosa M, Forastiere F, Rapiti E, Nardecchia B, Pistelli R. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J.* 1997;10(12):2794-800.

273. Alter P, Lucke T, Watz H, *et al.* Cardiovascular predictors of mortality and exacerbations in patients with COPD. *Sci Rep.* 2022;12(1):21882.
274. Jones PW, Müllerova H, Agusti A, *et al.* Cardiovascular Disease Does Not Predict Exacerbation Rate or Mortality in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2018;197(3):400-403.
275. Xu S, Ye Z, Ma J, Yuan T. The impact of chronic obstructive pulmonary disease on hospitalization and mortality in patients with heart failure. *Eur J Clin Invest.* 2021;51(1):e13402.
276. Raslan AS, Quint JK, Cook S. All-Cause, Cardiovascular and Respiratory Mortality in People with Type 2 Diabetes and Chronic Obstructive Pulmonary Disease (COPD) in England: A Cohort Study Using the Clinical Practice Research Datalink (CPRD). *Int J Chron Obstruct Pulmon Dis.* 2023;Volume 18:1207-1218.
277. Aune D, Huang W, Nie J, Wang Y. Hypertension and the Risk of All-Cause and Cause-Specific Mortality: An Outcome-Wide Association Study of 67 Causes of Death in the National Health Interview Survey. *Biomed Res Int.* 2021;2021:1-10.
278. Smith MC, Wrobel JP. Epidemiology and clinical impact of major comorbidities in patients with COPD. *Int J Chron Obstruct Pulmon Dis.* 2014;9:871-88.
279. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional Associations Between Clinically Relevant Depression or Anxiety and COPD: A Systematic Review and Meta-analysis. *Chest.* 2013;144(3):766-777.
280. Hernán MA, Alonso A, Logan R, *et al.* Observational Studies Analyzed Like Randomized Experiments: An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease. *Epidemiology.* 2008;19(6):766-779.
281. Sundh J, Magnuson A, Montgomery S, Andell P, Rindler G, Fröbert O. Beta-blockers to patients with Chronic Obstructive pulmonary disease (BRONCHIOLE) - Study protocol from a randomized controlled trial. *Trials.* 2020;21(1):123.
282. Pavasini R, Biscaglia S, d'Ascenzo F, *et al.* Antiplatelet Treatment Reduces All-Cause Mortality in COPD Patients: A Systematic Review and Meta-Analysis. *COPD.* 2016;13(4):509-14.
283. Aaron CP, Schwartz JE, Hoffman EA, *et al.* A Longitudinal Cohort Study of Aspirin Use and Progression of Emphysema-like Lung Characteristics on CT Imaging: The MESA Lung Study. *Chest.* 2018;154(1):41-50.
284. He Y, Zheng Y, Xu C, *et al.* Sertraline hydrochloride treatment for patients with stable chronic obstructive pulmonary disease complicated with depression: a randomized controlled trial. *Clin Respir J.* 2016;10(3):318-25.
285. Kunik ME, Roundy K, Veazey C, Soucek J, Richardson P, Wray NP, Stanley MA. Surprisingly High Prevalence of Anxiety and Depression in Chronic Breathing Disorders. *Chest.* 2005;127(4):1205-1211.
286. Yohannes AM, Alexopoulos GS. Pharmacological Treatment of Depression in Older Patients with Chronic Obstructive Pulmonary Disease: Impact on the Course of the Disease and Health Outcomes. *Drugs Aging.* 2014;31(7):483-492.
287. Visseren FLJ, Mach F, Smulders YM, *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* 2021;42(34):3227-3337.
288. McDonagh TA, Metra M, Adamo M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42(36):3599-3726.

289. Huebner ST, Henny S, Giezendanner S, *et al.* Prediction of Acute COPD Exacerbation in the Swiss Multicenter COPD Cohort Study (TOPDOCS) by Clinical Parameters, Medication Use, and Immunological Biomarkers. *Respiration*. 2022;101(5):441-454.
290. Jo YS, Kim YH, Lee JY, Kim K, Jung K-S, Yoo KH, Rhee CK. Impact of BMI on exacerbation and medical care expenses in subjects with mild to moderate airflow obstruction. *Int J Chron Obstruct Pulmon Dis*. 2018;Volume 13:2261-2269.
291. Green J, Bin Mahmood SU, Mori M, Yousef S, Mangi AA, Geirsson A. Stability across time of the neutrophil-lymphocyte and lymphocyte-neutrophil ratios and associations with outcomes in cardiac surgery patients. *J Cardiothorac Surg*. 2019;14(1):164.
292. Oshagbemi OA, Burden AM, Braeken DCW, *et al.* Stability of Blood Eosinophils in Patients with Chronic Obstructive Pulmonary Disease and in Control Subjects, and the Impact of Sex, Age, Smoking, and Baseline Counts. *Am J Respir Crit Care Med*. 2017;195(10):1402-1404.
293. Greulich T, Mager S, Lucke T, *et al.* Longitudinal stability of blood eosinophil count strata in the COPD COSYCONET cohort. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2999-3002.
294. Rodríguez-Hernández H, Simental-Mendía LE, Rodríguez-Ramírez G, Reyes-Romero MA. Obesity and inflammation: epidemiology, risk factors, and markers of inflammation. *Int J Endocrinol*. 2013;2013:678159.
295. Chung HY, Kim DH, Lee EK, *et al.* Redefining Chronic Inflammation in Aging and Age-Related Diseases: Proposal of the Senoinflammation Concept. *Aging Dis*. 2019;10(2):367-382.
296. Mentz RJ, Schmidt PH, Kwasny MJ, *et al.* The Impact of Chronic Obstructive Pulmonary Disease in Patients Hospitalized for Worsening Heart Failure With Reduced Ejection Fraction: An Analysis of the EVEREST Trial. *J Card Fail*. 2012;18(7):515-523.
297. Fisher KA, Stefan MS, Darling C, Lessard D, Goldberg RJ. Impact of COPD on the Mortality and Treatment of Patients Hospitalized With Acute Decompensated Heart Failure. *Chest*. 2015;147(3):637-645.

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