Chronic obstructive pulmonary disease: exacerbations and mortality

Prognostic value of biomarkers and comorbidities

JENS ELLINGSEN
Abstract

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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ISSN 1651-6206
ISBN 978-91-513-2044-1
URN urn:nbn:se:uu:diva-523303 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-523303)
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.


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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
FEV₁    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, 10th revision
ICS     inhaled corticosteroids
IHD     ischaemic heart disease
IQR     interquartile range
LABA    inhaled long-acting beta-2-agonist
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMA</td>
<td>inhaled long-acting muscarinic antagonist</td>
</tr>
<tr>
<td>LLN</td>
<td>lower limit of normal</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>mMRC</td>
<td>modified Medical Research Council dyspnoea scale</td>
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<tr>
<td>NAC</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>NLR</td>
<td>neutrophil-to-lymphocyte ratio</td>
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<tr>
<td>OCS</td>
<td>oral corticosteroids</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PLR</td>
<td>platelet-to-lymphocyte ratio</td>
</tr>
<tr>
<td>PRISm</td>
<td>preserved ratio, impaired spirometry</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SII</td>
<td>systemic immune-inflammation index</td>
</tr>
<tr>
<td>SIRI</td>
<td>systemic inflammation response index</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>SVC</td>
<td>slow vital capacity</td>
</tr>
<tr>
<td>TIE</td>
<td>Tools Identifying Exacerbations in COPD</td>
</tr>
<tr>
<td>V/Q</td>
<td>ventilation-perfusion</td>
</tr>
</tbody>
</table>
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.¹² 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.²⁶ During the 1970s, the role of smoking as a major cause of COPD was uncovered, with
Charles Fletcher as a key contributor. 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. 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. A milestone was the formation of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in the early 2000s. This also lead 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. With some modifications, those diagnostic criteria are still upheld by GOLD.

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.

It was first introduced in the GOLD 2023 report. 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).

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>COPD</td>
<td>Symptoms and history consistent with COPD and FEV1/FVC &lt; 0.7 after bronchodilation.</td>
</tr>
<tr>
<td>Early COPD</td>
<td>Pathobiological early COPD, regardless of the patient’s age.</td>
</tr>
<tr>
<td>Young COPD</td>
<td>COPD in a patient &lt; 50 years old.</td>
</tr>
<tr>
<td>Mild COPD</td>
<td>COPD with mild airflow obstruction, i.e., FEV1 &gt; 80% of predicted.</td>
</tr>
<tr>
<td>Pre-COPD</td>
<td>Clinical, radiological, or other findings suggestive of COPD, but FEV1/FVC ≥ 0.7.</td>
</tr>
<tr>
<td>PRISm</td>
<td>Preserved ratio, impaired spirometry, i.e., FEV1/FVC ≥ 0.7, but FEV1 &lt; 80% of predicted.</td>
</tr>
</tbody>
</table>

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

A few subgroups acknowledged by GOLD deserve mention (Table 1). 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 air-flow 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 FEV1/FVC > 0.7 but FEV1 < 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, initially proposed by Celli et al. 2022, 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. 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. 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. Disturbances in the airway microbiome may also be involved. 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.

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). 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. 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. 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.
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.⁴⁵,⁴⁹ 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.\(^4^0\) Also, emphysema \textit{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 \textit{hyperinflation} of the lungs – also called \textit{air trapping} – when they are not entirely emptied during expiration, i.e., when the end-expiratory volume increases.\(^4^1\) 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.\(^4^0\) 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.\(^4^0\) Hyperinflation is a significant cause of dyspnoea in COPD.\(^4^1\) 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.\(^3^9\)

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.\(^4^0\) 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.\(^4^0\) Pulmonary hypertension as a complication in COPD will increase dyspnoea,\(^3^6\) 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.\(^4^2\) 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.\(^4^3\) 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.\(^3^1\) The effects of smoking, lung hyperinflation, and hypoxia may be other sources of systemic inflammation.\(^4^4\) Regardless of its cause, systemic inflammation is thought to contribute to the extrapulmonary effects of COPD, such as sarcopenia and comorbidities, including heart diseases.\(^3^1,^4^4\)
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. Dyspnoea is usually chronic and progressive, worsens upon exertion, and causes disability. 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. Wheezing might be present, especially during exertion, and may be audible to the patient or only to a healthcare provider during auscultation. With increasing disease severity, symptoms such as weight loss and sarcopenia become more common. Symptoms might also arise from comorbidities such as osteoporosis, heart disease, depression, or anxiety.

1.6 Epidemiology
COPD is a common condition estimated to affect about 7% of adults living in Sweden. It is estimated by the Global Burden of Disease study that about 212 million people globally are living with COPD. Fortunately, the prevalence of COPD is decreasing worldwide, partly thanks to tobacco control programmes and improved housing, i.e., reduced indoor air pollution. 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 (FEV1/FVC < 0.7) is required by GOLD and in current Swedish guidelines. 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 FEV₁/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 FEV₁/FVC ratio is related to a reference for patient age, sex, and height, similar to how FEV₁ 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 FEV₁/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.

Another limitation of the FEV₁/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. 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 FEV₁/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.\textsuperscript{57} Despite these limitations, the fixed FEV1/FVC ratio is upheld.\textsuperscript{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).\textsuperscript{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.\textsuperscript{58,59}

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Alternate denomination</th>
<th>FEV1 % predicted after bronchodilation</th>
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<tbody>
<tr>
<td>GOLD 1</td>
<td>Mild</td>
<td>≥ 80%</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>≥ 50%, &lt; 80%</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>≥ 30%, &lt; 50%</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very severe</td>
<td>&lt; 30%</td>
</tr>
</tbody>
</table>

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.\textsuperscript{12,60} The CAT is probably the most used of these, in part because it is included in the graphics disseminated by GOLD.\textsuperscript{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.\textsuperscript{12}

Another validated tool that is widely used – thanks to its simplicity – is the modified Medical Research Council dyspnoea scale (mMRC).\textsuperscript{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.\textsuperscript{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 $\leq 1$ 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.

<table>
<thead>
<tr>
<th>Exacerbation history (number per year)</th>
<th>A</th>
<th>B</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 2$ AECOPDs, or $\geq 1$ leading to hospitalisation</td>
<td>CAT $&lt; 10$ and mMRC $&lt; 2$</td>
<td>CAT $\geq 10$ or mMRC $\geq 2$</td>
<td></td>
</tr>
<tr>
<td>$&lt; 2$ AECOPDs, none leading to hospitalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional parameters that might be considered at the time of diagnosis include:

1. **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.

2. **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).
   - N-terminal pro-brain natriuretic peptide, if HF is suspected.
α-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. 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.

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. 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, and the more severe the COPD, the more comorbidities. 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*. 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.]

Several other definitions have been used over the years. For a long time, the most prevalent definition was *an acute worsening of respiratory symptoms that results in additional therapy*. 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.

AECOPD severity is classified *post-factum* as mild, moderate, or severe, depending on the level of treatment. 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.

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. Moreover, AECOPDs accelerate lung function decline, decrease cardiovascular health, and increase mortality. The sequelae of AECOPDs are additive: the more AECOPDs a patient suffers, the worse the consequences are. There is also a risk of a negative spiral as AECOPDs *per se*, and many of their consequences, increase the risk of future AECOPDs. 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.

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. The increased inflammation worsens expiratory airflow limitation through mucosal oedema, mucus secretion, and increased smooth muscle constriction, which leads to exaggerated dynamic hyperinflation. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{102,103} It should be noted that these clusters are clinically indistinguishable.

Not all COPD patients suffer from AECOPDs; some rarely have one,\textsuperscript{104} and others have them frequently, i.e., ≥ 2 per year, referred to as the frequent exacerbator phenotype.\textsuperscript{105} Numerous risk factors of future AECOPDs have been described, of which the strongest is previous AECOPDs.\textsuperscript{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.\textsuperscript{58,70-72,106,107} Several biomarkers have been studied as predictors of AECOPDs (further reviewed in section 1.14 Biomarkers below),\textsuperscript{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.\textsuperscript{109} Others include increased cough, with or without increased and/or discoloured sputum, and wheezing.\textsuperscript{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.\textsuperscript{110} Hypoxaemia and hypercapnia may develop.

The work-up of a suspected AECOPD starts with a careful history and clinical examination.\textsuperscript{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 \(\text{FEV}_1\), 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 \(\text{FEV}_1\), 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. \cite{127-129} Interestingly, there is also evidence that the beneficial effect of ICS is greater for people with higher B-Eos, \cite{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. \cite{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. \cite{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). \cite{131-137} Several of these studies have been criticised, \cite{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) \cite{141} and the beta-blocker metoprolol did not reduce mortality \cite{142} 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. \cite{143} The list is not exhaustive.

<table>
<thead>
<tr>
<th>Tool</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADO</td>
<td>Age, dyspnoea (mMRC), airflow obstruction (FEV$_1$)</td>
</tr>
<tr>
<td>B-AE-D</td>
<td>BMI, AECOPD, dyspnoea (mMRC)</td>
</tr>
<tr>
<td>BODE</td>
<td>BMI, airflow obstruction (FEV$_1$), dyspnoea (mMRC), exercise capacity (6MWT)</td>
</tr>
<tr>
<td>e-BODE</td>
<td>AECOPD, BMI, airflow obstruction (FEV$_1$), dyspnoea (mMRC), exercise capacity (6MWT)</td>
</tr>
<tr>
<td>BODEx</td>
<td>BMI, airflow obstruction (FEV$_1$), dyspnoea (mMRC), AECOPD</td>
</tr>
<tr>
<td>DOSE</td>
<td>Dyspnoea (mMRC), airflow obstruction (FEV$_1$), current smoking, AECOPD</td>
</tr>
<tr>
<td>SAFE</td>
<td>Saint George’s Respiratory Questionnaire score, airflow obstruction (FEV$_1$), exercise capacity (6MWT)</td>
</tr>
</tbody>
</table>

**Abbreviations:** COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council dyspnoea scale; FEV$_1$, 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, \cite{144,145} the BODE (and modified versions e-BODE and BODEx), \cite{144,146,147} the DOSE indices, \cite{148} and others (Table 4). \cite{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, but the ADO index performs best. 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. It includes specified comorbidities (HF, coronary artery disease, hypertension, and diabetes) and four other factors (mMRC score, FEV$_1$, age, and body mass index [BMI]) that are significant predictors of mortality. The algorithm allocates COPD patients to five groups, with different mortality risks. In two subsequent studies, the algorithm was validated for mortality prediction in other populations and over extended follow-up periods.

There have been several attempts to develop prognostic tools for AECOPDs, but none is currently recommended by GOLD (except taking AECOPD history). However, the ACCEPT (Acute COPD Exacerbation Prediction Tool) is a promising online tool. 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. 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:

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

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. Over the years, several other phenotypes have been proposed, with the frequent exacerbator phenotype being one of the most established. 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).\textsuperscript{158} This concept refers to ‘[…] a subtype of a (clinical) condition defined by a distinct pathophysiological mechanism’.\textsuperscript{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.\textsuperscript{160} Other proposed endotypes include neutrophilic COPD\textsuperscript{161} and eosinophilic COPD,\textsuperscript{162} although controversy exists.\textsuperscript{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.

![Image](image.png)


Recognising the complexity of COPD (and asthma) and the difficulties sorting patients into ‘boxes’ of phenotypes or endotypes, the concept of \textit{treatable traits} has been developed (Figure 5).\textsuperscript{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.\textsuperscript{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. 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
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.\textsuperscript{170} The acute-phase response is highly non-specific and can be induced by almost any inflammation, infection, tissue damage, or neoplasia.\textsuperscript{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.\textsuperscript{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.\textsuperscript{170} On its own, it is of limited value.

CRP is higher in people with COPD than in healthy controls,\textsuperscript{42,168} and elevated levels are associated with increased risk of cardiovascular diseases and COPD mortality.\textsuperscript{108,171,172} Moreover, CRP has been studied during AECOPDs as a tool to diagnose AECOPD\textsuperscript{173} and determine the need for antibiotics.\textsuperscript{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\textsuperscript{99,169,175} or applies only to severe AECOPDs.\textsuperscript{176-178} Two studies have reported that CRP in combination with other biomarkers are prognostic of AECOPDs;\textsuperscript{168,179} Agustí et al. used CRP, B-Leu, interleukin-6, and fibrinogen combined,\textsuperscript{168} whereas Thomsen et al. used CRP, B-Leu, and fibrinogen combined\textsuperscript{179} 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.\textsuperscript{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.\textsuperscript{180}

Fibrinogen links platelets by binding to the glycoprotein receptor GP IIb/IIIa, expressed on activated platelets, i.e., fibrinogen promotes platelet
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. 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. Moreover, elevated fibrinogen is associated with increased mortality risk, and several studies have found it to be prognostic of moderate/severe AECOPDs or severe AECOPDs. However, some authors have reported conflicting results. As noted in the section on CRP above, fibrinogen, in combination with other biomarkers, predicts AECOPDs. 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. 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. 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. Smoking makes platelets more prone to aggregation, and data suggest that platelets are involved in the pathogenesis of COPD. Moreover, mean levels of blood platelets (B-Plt) are higher in COPD than in controls. There is also evidence that B-Plt activation is higher in stable COPD than in healthy controls and even higher in AECOPDs. 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. 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.

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, and the levels seem to increase with the severity of airflow obstruction. Higher B-Leu are associated with an increased mortality risk in COPD. Regarding the prediction of AECOPDs, data are conflicting. Association with an increased AECOPD risk has been reported, although other studies found no association when confounders were considered. As noted in the section on CRP above, B-Leu, in combination with other biomarkers, predict AECOPDs.

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. Neutrophils release proteases, reactive oxygen species, and neutrophil extracellular traps, and contribute to pro-inflammatory signalling. Their role in the development of emphysema and mucus hypersecretion is well-established. Reports suggest that neutrophil dysfunction may be a critical pathobiological mechanism and that there may be interactions between neutrophilic inflammation and the airway microbiome.

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

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. Blood lymphocytes (B-Lym) have an altered subtype distribution in COPD compared with healthy controls. Moreover, levels of B-Lym are lower, and the longitudinal B-Lym decrease is greater in people with COPD than in healthy smokers. COPD patients with declining B-Lym have a higher incidence of cancer and increased mortality risk, and low B-Lym are associated with increased mortality risk, faster FEV₁ decline, lower quality of life, and worse exercise capacity. Low B-Lym are associated with increased mortality also in the general population.
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. 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. A significant proportion of AECOPDs are characterised by eosinophilic inflammation. 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. B-Eos correlate with eosinophilic inflammation in the lung. The results of observational studies on the ability of B-Eos to predict AECOPDs are conflicting, where some have found levels to be prognostic whereas others found no such association. Some authors have noted increased mortality in COPD patients with high B-Eos, but others report the opposite. 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, BMI, comorbid asthma, smoking status, ICS use, and OCS use. 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. On the other hand, studies show fair longitudinal stability of B-Eos measurements in COPD.

It should be noted that ‘high’ in the context of B-Eos and COPD often refers to values above 0.15–0.3 ×10^9 cells/L, which is usually well within normal. All Swedish laboratories are recommended to use < 0.5 ×10^9 cells/L as a reference range. As mentioned above, B-Eos is recommended by GOLD as a predictive biomarker of response to ICS therapy, 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.

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. There are different subsets of monocytes with partly different but overlapping functions. Depending on the microenvironment, monocytes may differentiate into dendritic cells or macrophages. The latter are believed to be of significance in COPD. 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. One study has found that B-Mon measured during stable-phase COPD are independently associated with future AECOPDs.

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. 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. In COPD, NLR is higher than in healthy controls and further increased in AECOPDs. At admission, NLR can predict a diagnosis of AECOPD, and NLR obtained during AECOPD or hospitalisation can predict outcomes such as the need for readmission and mortality. PLR obtained at admission predicts mortality in AECOPD, and one study has suggested that PLR measured during stable-phase COPD can predict future AECOPDs.

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. PLR obtained at admission predicts mortality in AECOPD, and one study has suggested that PLR measured during stable-phase COPD can predict future AECOPDs.

The systemic immune-inflammation index (SII), the systemic inflammation response index (SIRI), and the aggregate index of systemic inflammation (AISI) are novel biomarkers. They are calculated as follows: SII = B-Neu × B-Plt / B-Lym; SIRI = B-Neu × B-Mon / B-Lym; AISI = B-Neu × B-Plt × B-Mon / B-Lym. Although these indices have been studied in other diseases, only a few publications concerning COPD exist. SII has been associated with increased mortality risk in COPD and AISI with increased mortality in COPD patients hospitalised due to covid-19. The same report indicating an association between PLR and future AECOPDs also reported that SII and SIRI were associated with AECOPDs.
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. 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 FEV$_1$ 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. FEV₁, SVC, and FVC (litres) were obtained; the former was also expressed as per cent predicted based on Swedish reference values.

3.4.5 Symptoms
In PATHOS, there were no data on symptoms.

In TIE, symptoms were assessed with the mMRC and the CAT. An mMRC score ≥ 2 and/or a CAT score ≥ 10 were considered a high burden of symptoms. 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.\textsuperscript{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 ≥ 0.3 ×10^9 cells/L proposed by GOLD. B-Bas was dichotomised after the upper quartile of the TIE population (≥ 0.09 ×10^9 cells/L) as the laboratory’s upper reference value (> 0.1 ×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 ≥ 1.8 ×10^9 cells/L suggested by Semenzato et al.

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. 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. 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).
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) 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 agonists; LABAs, long-acting beta-2-agonists; ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; SSRIs, selective serotonin reuptake inhibitors.
<table>
<thead>
<tr>
<th>Condition</th>
<th>aHR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.02</td>
<td>(1.01–1.02)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pneumonias&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.88</td>
<td>(1.74–2.04)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.40</td>
<td>(1.24–1.58)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1.18</td>
<td>(1.06–1.32)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.52</td>
<td>(1.40–1.64)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.90</td>
<td>(0.84–0.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.13</td>
<td>(1.03–1.23)</td>
<td>0.008</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.10</td>
<td>(0.97–1.24)</td>
<td>0.137</td>
</tr>
<tr>
<td>Fractures&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.07</td>
<td>(1.04–1.10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.70</td>
<td>(0.64–0.76)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Charlson comorbidity index&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.12</td>
<td>(1.09–1.14)</td>
<td>&lt; 0.001</td>
</tr>
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**Any use of the drug class**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>aHR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMAs</td>
<td>1.07</td>
<td>(0.98–1.18)</td>
<td>0.138</td>
</tr>
<tr>
<td>LABAs</td>
<td>0.87</td>
<td>(0.75–1.00)</td>
<td>0.055</td>
</tr>
<tr>
<td>ICS/LABAs, fixed combination</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>0.90</td>
<td>(0.82–0.98)</td>
<td>0.022</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>1.16</td>
<td>(1.08–1.25)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>1.29</td>
<td>(1.17–1.43)</td>
<td>&lt; 0.001</td>
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<td>ACEis</td>
<td>0.82</td>
<td>(0.73–0.93)</td>
<td>0.002</td>
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<tr>
<td>Beta-blockers</td>
<td></td>
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<td>ARBs</td>
<td>0.85</td>
<td>(0.79–0.92)</td>
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<td>Diuretics</td>
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<td>(1.26–1.48)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>0.65</td>
<td>(0.60–0.71)</td>
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<tr>
<td>Bisphosphonates</td>
<td>1.21</td>
<td>(1.05–1.40)</td>
<td>0.010</td>
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<tr>
<td>SSRIs</td>
<td>0.82</td>
<td>(0.75–0.90)</td>
<td>&lt; 0.001</td>
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**Relative exposure to the drug class**

<table>
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<th>aHR</th>
<th>95% CI</th>
<th>p-value</th>
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</thead>
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<td>ICS</td>
<td>0.79</td>
<td>(0.66–0.94)</td>
<td>0.008</td>
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<td>LAMAs</td>
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<td>(1.14–1.55)</td>
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<tr>
<td>LABAs</td>
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<td>(0.97–1.61)</td>
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<td>ICS/LABAs, fixed combination</td>
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<td>(0.61–1.08)</td>
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<tr>
<td>N-acetylcysteine</td>
<td>1.26</td>
<td>(1.08–1.48)</td>
<td>0.004</td>
</tr>
<tr>
<td>Oral steroids</td>
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<td></td>
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</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.87</td>
<td>(0.77–0.98)</td>
<td>0.022</td>
</tr>
<tr>
<td>ACEis</td>
<td></td>
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<tr>
<td>Beta-blockers</td>
<td>0.86</td>
<td>(0.76–0.97)</td>
<td>0.016</td>
</tr>
<tr>
<td>ARBs</td>
<td></td>
<td></td>
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<tr>
<td>Diuretics</td>
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<td>Statins</td>
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<tr>
<td>Bisphosphonates</td>
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<tr>
<td>SSRIs</td>
<td>0.70</td>
<td>(0.56–0.87)</td>
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</tbody>
</table>
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.](image-url)
Table 6. Relative mortality risk in the TIE study (Paper IV). Cox proportional hazards models of the association between clinical COPD phenotypes and mortality

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Unadjusted (n = 566)</th>
<th>Adjusted* (n = 564)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>1, severe comorbid</td>
<td>8.24</td>
<td>1.93–35.3</td>
</tr>
<tr>
<td>2, mixed respiratory/comorbid</td>
<td>2.91</td>
<td>0.66–12.9</td>
</tr>
<tr>
<td>3, asymptomatic comorbid/obese</td>
<td>6.26</td>
<td>1.40–28.0</td>
</tr>
<tr>
<td>4, very severe respiratory</td>
<td>16.7</td>
<td>3.25–86.3</td>
</tr>
<tr>
<td>5, mild respiratory</td>
<td>ref</td>
<td>ref</td>
</tr>
</tbody>
</table>

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 ± 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.

<table>
<thead>
<tr>
<th>Models with NLR only&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Models with B-Eos only&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Models combining NLR and B-Eos&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
</tr>
<tr>
<td>NLR, continuous</td>
<td>x x</td>
<td>1.22 1.06–1.40</td>
</tr>
<tr>
<td>NLR, ≥ 3.00 vs &lt; 3.00</td>
<td>1.13 0.76–1.68</td>
<td>1.13 0.76–1.67</td>
</tr>
<tr>
<td>B-Eos, continuous&lt;sup&gt;c&lt;/sup&gt;</td>
<td>x x</td>
<td>1.08 0.98–1.20</td>
</tr>
<tr>
<td>B-Eos, ≥ 0.3 vs &lt; 0.3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>x x</td>
<td>1.54 1.06–2.24</td>
</tr>
</tbody>
</table>

Notes: x indicates predictor not analysed. Models adjusted for ≥ 1 AECOPD in the preceding year, CAT score, BMI, current smoking, current ICS use, FEV<sub>1</sub>, 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<sup>9</sup> cells/L increase. d) ×10<sup>9</sup> 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; FEV<sub>1</sub>, 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 ± 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 percent 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, FEV<sub>1</sub>, 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 ×10<sup>9</sup> 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.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>n</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, per 1 mg/L</td>
<td>565</td>
<td>1.02</td>
<td>0.99–1.04</td>
</tr>
<tr>
<td>CRP ≥ 5 mg/L</td>
<td>565</td>
<td><strong>1.86</strong></td>
<td><strong>1.29–2.67</strong></td>
</tr>
<tr>
<td>Fibrinogen, per 1 g/L</td>
<td>545</td>
<td><strong>1.59</strong></td>
<td><strong>1.26–2.00</strong></td>
</tr>
<tr>
<td>Fibrinogen ≥ 3.5 g/L</td>
<td>545</td>
<td><strong>2.01</strong></td>
<td><strong>1.45–2.79</strong></td>
</tr>
<tr>
<td>Leukocytes, per 1 ×10⁹ cells/L</td>
<td>568</td>
<td><strong>1.16</strong></td>
<td><strong>1.08–1.24</strong></td>
</tr>
<tr>
<td>Leukocytes &gt; 9 ×10⁹ cells/L</td>
<td>568</td>
<td><strong>2.18</strong></td>
<td><strong>1.52–3.13</strong></td>
</tr>
<tr>
<td>Platelets, per 100 ×10⁹ cells/L</td>
<td>547</td>
<td><strong>1.36</strong></td>
<td><strong>1.07–1.71</strong></td>
</tr>
<tr>
<td>Platelets &gt; 350 ×10⁹ cells/L</td>
<td>547</td>
<td>1.42</td>
<td>0.86–2.37</td>
</tr>
<tr>
<td>Neutrophils, per 1 ×10⁹ cells/L</td>
<td>564</td>
<td><strong>1.23</strong></td>
<td><strong>1.12–1.36</strong></td>
</tr>
<tr>
<td>Neutrophils &gt; 5.4 ×10⁹ cells/L</td>
<td>564</td>
<td><strong>1.92</strong></td>
<td><strong>1.36–2.71</strong></td>
</tr>
<tr>
<td>Lymphocytes, per 1 ×10⁹ cells/L</td>
<td>562</td>
<td>0.90</td>
<td>0.73–1.11</td>
</tr>
<tr>
<td>Lymphocytes ≥ 1.8 ×10⁹ cells/L</td>
<td>562</td>
<td>0.96</td>
<td>0.69–1.33</td>
</tr>
<tr>
<td>Monocytes, per 0.1 ×10⁹ cells/L</td>
<td>562</td>
<td><strong>1.10</strong></td>
<td><strong>1.03–1.18</strong></td>
</tr>
<tr>
<td>Monocytes &gt; 0.8 ×10⁹ cells/L</td>
<td>562</td>
<td><strong>1.81</strong></td>
<td><strong>1.17–2.81</strong></td>
</tr>
<tr>
<td>PLR, per 100 units</td>
<td>541</td>
<td><strong>1.32</strong></td>
<td><strong>1.02–1.71</strong></td>
</tr>
<tr>
<td>PLR ≥ 169.1</td>
<td>541</td>
<td>1.20</td>
<td>0.83–1.73</td>
</tr>
<tr>
<td>SII, per 100 units</td>
<td>541</td>
<td><strong>1.08</strong></td>
<td><strong>1.04–1.12</strong></td>
</tr>
<tr>
<td>SII ≥ 856</td>
<td>541</td>
<td><strong>1.52</strong></td>
<td><strong>1.05–2.19</strong></td>
</tr>
<tr>
<td>SIRI, per 1 unit</td>
<td>562</td>
<td><strong>1.28</strong></td>
<td><strong>1.12–1.47</strong></td>
</tr>
<tr>
<td>SIRI ≥ 2.024</td>
<td>562</td>
<td><strong>1.76</strong></td>
<td><strong>1.23–2.52</strong></td>
</tr>
<tr>
<td>AISI, per 100 units</td>
<td>541</td>
<td><strong>1.09</strong></td>
<td><strong>1.04–1.14</strong></td>
</tr>
<tr>
<td>AISI ≥ 533.7</td>
<td>541</td>
<td><strong>2.03</strong></td>
<td><strong>1.40–2.92</strong></td>
</tr>
</tbody>
</table>

**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 ± 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.
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.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Unadjusted (n = 566)</th>
<th>Adjusted* (n = 564)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>1, severe comorbid</td>
<td>3.04</td>
<td>1.93–4.79</td>
</tr>
<tr>
<td>2, mixed respiratory/comorbid</td>
<td>2.38</td>
<td>1.54–3.66</td>
</tr>
<tr>
<td>3, asymptomatic comorbid/obese</td>
<td>1.13</td>
<td>0.66–1.94</td>
</tr>
<tr>
<td>4, very severe respiratory</td>
<td>3.52</td>
<td>1.73–7.15</td>
</tr>
<tr>
<td>5, mild respiratory</td>
<td>ref</td>
<td>ref</td>
</tr>
</tbody>
</table>

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/µL to ×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.

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

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.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>Phenotype 1 vs 5 aOR</th>
<th>95% CI</th>
<th>Phenotype 2 vs 5 aOR</th>
<th>95% CI</th>
<th>Phenotype 3 vs 5 aOR</th>
<th>95% CI</th>
<th>Phenotype 4 vs 5 aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &gt; 350*</td>
<td>541</td>
<td>1.22</td>
<td>0.52–2.86</td>
<td>0.68</td>
<td>0.31–1.48</td>
<td>0.41</td>
<td>0.13–1.28</td>
<td>0.45</td>
<td>0.05–3.82</td>
</tr>
<tr>
<td>Leukocytes &gt; 9*</td>
<td>562</td>
<td><strong>6.56</strong></td>
<td><strong>2.92–14.7</strong></td>
<td><strong>2.50</strong></td>
<td><strong>1.19–5.25</strong></td>
<td><strong>3.00</strong></td>
<td><strong>1.26–7.15</strong></td>
<td>1.29</td>
<td>0.25–6.68</td>
</tr>
<tr>
<td>Neutrophils &gt; 5.4*</td>
<td>558</td>
<td><strong>3.78</strong></td>
<td><strong>1.86–7.68</strong></td>
<td>1.76</td>
<td>0.94–3.32</td>
<td><strong>2.20</strong></td>
<td><strong>1.04–4.68</strong></td>
<td>1.51</td>
<td>0.41–5.54</td>
</tr>
<tr>
<td>Eosinophils ≥ 0.3*</td>
<td>556</td>
<td>0.92</td>
<td>0.48–1.75</td>
<td>0.77</td>
<td>0.44–1.34</td>
<td>0.83</td>
<td>0.43–1.63</td>
<td>0.32</td>
<td>0.07–1.55</td>
</tr>
<tr>
<td>Lymphocytes ≥ 1.8*</td>
<td>556</td>
<td><strong>1.99</strong></td>
<td><strong>1.09–3.63</strong></td>
<td>1.57</td>
<td>0.94–2.60</td>
<td><strong>2.44</strong></td>
<td><strong>1.29–4.63</strong></td>
<td>0.74</td>
<td>0.25–2.21</td>
</tr>
<tr>
<td>Monocytes &gt; 0.8*</td>
<td>556</td>
<td><strong>6.24</strong></td>
<td><strong>2.23–17.5</strong></td>
<td>2.03</td>
<td>0.74–5.51</td>
<td><strong>3.98</strong></td>
<td><strong>1.36–11.6</strong></td>
<td>1.06</td>
<td>0.11–9.90</td>
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<tr>
<td>Basophils ≥ 0.09*</td>
<td>556</td>
<td>0.95</td>
<td>0.49–1.82</td>
<td>0.91</td>
<td>0.52–1.59</td>
<td>1.09</td>
<td>0.56–2.12</td>
<td>0.34</td>
<td>0.07–1.64</td>
</tr>
<tr>
<td>NLR ≥ 3.1</td>
<td>556</td>
<td>1.50</td>
<td>0.76–2.96</td>
<td>0.75</td>
<td>0.40–1.40</td>
<td>1.27</td>
<td>0.62–2.61</td>
<td>1.40</td>
<td>0.42–4.70</td>
</tr>
<tr>
<td>PLR ≥ 169,1</td>
<td>535</td>
<td>0.81</td>
<td>0.41–1.59</td>
<td>0.82</td>
<td>0.46–1.46</td>
<td>0.90</td>
<td>0.45–1.78</td>
<td>1.23</td>
<td>0.37–4.04</td>
</tr>
<tr>
<td>SII ≥ 856</td>
<td>535</td>
<td>1.57</td>
<td>0.79–3.13</td>
<td>0.81</td>
<td>0.43–1.51</td>
<td>1.21</td>
<td>0.59–2.51</td>
<td>1.56</td>
<td>0.46–5.31</td>
</tr>
<tr>
<td>SIRI ≥ 2.024</td>
<td>556</td>
<td><strong>3.63</strong></td>
<td><strong>1.67–7.90</strong></td>
<td>1.50</td>
<td>0.73–3.11</td>
<td><strong>2.65</strong></td>
<td><strong>1.17–6.01</strong></td>
<td>2.73</td>
<td>0.75–9.89</td>
</tr>
<tr>
<td>AISI ≥ 533</td>
<td>535</td>
<td><strong>4.29</strong></td>
<td><strong>1.98–9.28</strong></td>
<td>1.49</td>
<td>0.73–3.03</td>
<td><strong>2.28</strong></td>
<td><strong>1.00–5.16</strong></td>
<td>2.17</td>
<td>0.57–8.34</td>
</tr>
<tr>
<td>CRP ≥ 5 mg/L</td>
<td>559</td>
<td><strong>8.76</strong></td>
<td><strong>3.55–21.6</strong></td>
<td><strong>4.22</strong></td>
<td><strong>1.82–9.77</strong></td>
<td><strong>4.88</strong></td>
<td><strong>1.89–12.6</strong></td>
<td><strong>6.50</strong></td>
<td><strong>1.72–24.5</strong></td>
</tr>
<tr>
<td>Fibrinogen ≥ 3.5 g/L</td>
<td>539</td>
<td><strong>3.93</strong></td>
<td><strong>2.12–7.27</strong></td>
<td>1.53</td>
<td>0.93–2.53</td>
<td>1.39</td>
<td>0.75–2.58</td>
<td><strong>6.90</strong></td>
<td><strong>1.80–26.4</strong></td>
</tr>
</tbody>
</table>

Notes: Bolded text indicates statistical significance (1 is not included in the 95% CI). * × 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. Similarly, there were data on smoking history, also a significant risk factor, for only a minority. Data on BMI and vaccination status were also lacking.

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), 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). 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). 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, and Paper I was a substantial contribution.

In Paper IV, we confirmed that the algorithm initially proposed by Burgel et al. 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, although a few studies report contradicting results. A meta-analysis published in 2020 concluded that comorbid HF increases COPD mortality, whereas a 2021 meta-analysis concluded that comorbid COPD increases HF mortality.

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, but not all. 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. 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.

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. A more probable explanation is that hypertension – like many other comorbidities – is underdiagnosed in COPD, 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{129}

Previous observational studies on beta-blockers have indicated an association with improved survival in COPD.\textsuperscript{135} However, a critical review has identified several sources of bias that may have exaggerated the results.\textsuperscript{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.\textsuperscript{142} Our results aligned with those of previous observational studies and – pending results from future RCTs\textsuperscript{281} – 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.\textsuperscript{191} Previous observational studies have suggested benefits of ASA,\textsuperscript{136,282} but the results have been criticised.\textsuperscript{138} A longitudinal study reported that COPD patients treated with ASA had a slower progression of emphysema than those without ASA.\textsuperscript{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.\textsuperscript{284} A more plausible explanation is that adequate treatment of otherwise underdiagnosed and undertreated mental illnesses\textsuperscript{285} 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.\textsuperscript{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.\textsuperscript{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 $\geq 5$ 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 biomarkers168,179 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 FEV$_1$ $\geq 50\%$ 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 $\geq 3.5 \text{ g/L}$ was associated with a 50% increase in AECOPD risk after adjustment for confounders, in accordance with previous results.\textsuperscript{108,181-184} Others have found fibrinogen to be associated with AECOPDs in unadjusted analyses only,\textsuperscript{99,169} or with severe AECOPDs only.\textsuperscript{178,185} Moreover, fibrinogen analysed in combination with other biomarkers is prognostic of AECOPDs.\textsuperscript{168,179} In summary, the evidence from our work and that of others indicates that fibrinogen $\geq 3.5 \text{ g/L}$ is independently prognostic of future AECOPDs. Future analyses should examine if incorporating fibrinogen in composite tools enhances predictions.

B-Leu $> 9 \times 10^9 \text{ cells/L}$ were associated with a 65% increase in AECOPD risk. This aligns with two previous reports, although they used continuous B-Leu.\textsuperscript{99,185} Others have reported associations only in unadjusted analyses.\textsuperscript{175,193} A meta-analysis including three studies found no association between B-Leu and future AECOPD.\textsuperscript{108} However, B-Leu analysed in combination with other biomarkers have been shown to predict AECOPDs.\textsuperscript{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.\textsuperscript{258} However, that study did not adjust for the strongest risk factor: AECOPD history.\textsuperscript{58} PLR is higher in AECOPD than in stable COPD,\textsuperscript{190} and previous AECOPDs are associated with higher B-Plt.\textsuperscript{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.\textsuperscript{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, and future AECOPDs in time-to-event analyses. The items included in the algorithm are established risk factors for AECOPDs, although regarding BMI, being underweight is probably a stronger risk factor than having a BMI < 30 kg/m², 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, 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, 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. ACCEPT seems closest to clinical acceptance and has the advantage of individual risk prediction through statistical calculations. 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.
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 (≥ 0.3 ×10⁹ cells/L) B-Eos in Paper II, and 22% had persistently low (< 0.15 ×10⁹ 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.\textsuperscript{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.\textsuperscript{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 FEV\textsubscript{1} would have resulted in associations between phenotype 4 and more of the biomarkers, reflecting systemic inflammation as a feature of COPD.\textsuperscript{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.\textsuperscript{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.\cite{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,\cite{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.\cite{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.\cite{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.\textsuperscript{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,\textsuperscript{138} i.e., primary prevention of cardiovascular events. An emulated trial based on observational data could be considered.\textsuperscript{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.\textsuperscript{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.
Målet med denna avhandling har varit att undersöka faktorer som kan förut-säga försämringsepisoder och död hos patienter med kroniskt obstruktiv lung-sjukdom (KOL). Ett särskilt fokus har legat på samsjuklighet, det vill säga förekomst av andra sjukdomar parallellt med KOL, och inflammatoriska bio-markörer. Det sistnämnda är blodprover som återspeglar graden av inflammato-riskt påslag i kroppen.


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 kortisontabletter och antibiotika.

För att kunna förebygga negativa händelser som exacerbationer och förhindra 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 delarbete.


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 inbjudits 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 förutsäga 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 vårdet 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, där- ibland 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.
9 Acknowledgements

I wish to express my gratitude to all the people without whom the works presented in this thesis would never have been possible:

Professors Andrei Malinovschi and Christer Janson, my supervisors and the dynamic duo of respiratory research. Thank you for your patient support and continuous encouragement throughout this long journey. As supervisors, you complement each other and make the perfect team. It has been a true privilege to learn from you, and I look forward to continuing our cooperation.

My co-authors, Kristina Bröms, Amir Farkhooy, Gunnar Johansson, Maria Härdstedt, Marieann Högman, Karin Lisspers, Andreas Palm, Björn Stållberg, and Marcus Thuresson. You have patiently reviewed every little piece of text I have written, and it got better every time. Thank you for sharing your broad experience and reminding me that everything can be improved.

My deepest gratitude to all the fantastic COPD patients participating the studies by us and others. Without your generous contributions, there would be no scientific advances. And no thesis.

All the staff involved in the TIE study. Thank you for doing the hard work of collecting data and taking care of the participants.

Professor Eva Lindberg, master of navigating the academic world. Thanks for teaching me to avoid the boring parts and enjoy the festive side of science – the oysters in Milan were terrific! – and for always finding an opportunity for a get-together.

The one and only Gun-Marie “Gunnis” Bodman Lund. Your endless support with all the practical stuff has been invaluable. Thanks also for all our joyful chats by the tea-pot and all our travels to congresses all across Europe.

All the other staff at the Lung, Allergy & Sleep Research department. Thank you for all the scientific and non-scientific lunch room chats, and for your travel company in Tallinn, Milan, Copenhagen, and all the other places we have travelled to.
My clinical mentors and idols: Gustav Broman, Inger Dahlén, Kristina Lamberg, Carl-Axel Karlsson, and Mary Kämpe. I am deeply indebted to you for showing me how to be a pulmonologist. Together, you know everything that is worth knowing about respiratory medicine, and I can think of no better team of teachers. I try to be as brilliant as you.

Thanks also to Even Høye, who together with Andreas Palm – a long time ago in a galaxy far, far away – planted the idea of pulmonology in my mind with their ridiculous jokes about sudokus.

All my wonderful colleagues in scrubs, thank you for being the reason I don’t break up with the hospital. PhD role models and fellow Successors of oversized shoes Shadi Hägg, Mirjam Ljunggren, and Fredrik Sundbom. Playmates Össur Emilsson and Emil Ekbom. Luminous lung cancer fighters Erik Broström, Sebastian Gagatek, and Stéphanie Mindus. Fabulous physios Micke Andersson, Karin Ersson, Henrik Johansson, and Reka Markaszne Kammerer. All the others not mentioned here: thank you, too!

Fellow metalhead, the karate dad Niclas Abrahamsson, and our clinical compadres who have left the main building: Kirti Chetty, Martin Sandelin, Gabriel Westman, Martin Wohlin, and Axel Åkerblom. It is always too long since the last beer.

Longtime friends from med school, Per Granström, Jakob Järhult, Staffan Thorling, and Jonas Wixner. Almost half-way through to retirement now, but still the same dudes. Let’s have a fraction of the Bowmore Enigma! And he who will never be retired, my dearest friend and fellow Cohen fan, the late David Johansson. Loved and missed, gone too soon. There is a crack, a crack in everything, that’s how the light gets in.

My parents Anders Ellingsen and Eva Lidén, I am very grateful that you gave me the opportunity to become whatever I wanted to be by raising me with loads of novels, knowledge, and curiosity.

My late grandmother Ingeborg Ellingsen, whose rheumatism made me want to become a doctor when I was a kid.

Most of all, my wife Malin Hemmingsson, and our children Sonja and Oskar. Thank you for putting up with all my sitting in front of the computer and coming home late from work. You are the loves of my life.
10 References

4. Laënnec RT. *De l’auscultation médiate, on traité du diagnostic des maladies des poumons et du coeur*. Brosson & Chaudé; 1819.
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;


92. Kim V, Aaron SD. What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement. Eur Respir J. 2018;52(5)


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