

Chronic Obstructive Pulmonary Disease and the Management of Cardiopulmonary Risk in the UK: A Systematic Literature Review and Modified Delphi Study

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Abstract: Chronic obstructive pulmonary disease (COPD) is linked to increased mortality and morbidity, especially in patients with coexisting cardiovascular disease. These patients face heightened cardiopulmonary risk, which escalates further after acute exacerbations of COPD. While there is some guidance on the management of acute exacerbations of COPD, there is a lack of specific strategies for addressing cardiopulmonary risk in COPD. This program of work aimed to establish UK consensus statements and a clinical pathway for managing cardiopulmonary risk in patients with COPD, synthesizing evidence and expert input through a modified Delphi approach. A multidisciplinary Taskforce conducted a systematic review, focusing on the UK and addressing questions relating to the healthcare burden of acute exacerbations of COPD (AECOPDs), the link between AECOPDs and cardiopulmonary events, the management of cardiopulmonary risk in patients with COPD, and the guidelines and interventions implemented to optimize COPD management. The evidence identified was summarized and used to synthesize preliminary consensus statements reflecting the current situation and recommendations for action. Following iterative voting rounds, consensus was reached on 18 statements. Further to this, a clinical pathway framework to support the recognition and management of cardiopulmonary risk in patients with COPD using the consensus statements was formulated. AECOPDs were identified as a substantial healthcare burden in the UK, contributing to high mortality, frequent healthcare interactions, and elevated costs. These exacerbations were associated with cardiopulmonary events such as myocardial infarction and stroke. Most UK guidelines have focused on the respiratory management of COPD exacerbations, but lack strategies to specifically address cardiopulmonary risk, highlighting the need for integration of care. This consensus program has identified gaps in management, as well as a need to optimize care and reduce the cost of COPD management through the development of new UK policies and clinical guidance.

Keywords: COPD, cardiovascular disease, United Kingdom, interdisciplinary health teams

Introduction

Chronic obstructive pulmonary disease (COPD) is the fifth-leading cause of premature death in the UK, with over 21,000 COPD-related deaths annually.^{1–3} It is the second-largest cause of emergency hospitalization in the UK, with one in eight admissions attributed to COPD.⁴ Compared with the general population, patients with COPD have nearly twice as many chronic comorbidities, which are key contributors to morbidity and mortality in this population.^{5,6} More specifically, patients with COPD face a 2- to 4-fold increased risk of mortality related to cardiovascular disease (CVD) compared with those without COPD, and CVD is a leading cause of hospitalization among patients with COPD, accounting for nearly half of hospital admissions in this population.⁵

Cardiopulmonary risk is defined as the risk of serious respiratory and/or cardiovascular events in patients with COPD.^{7–9} These include, but are not limited to, COPD exacerbations, myocardial infarction (MI), stroke, heart failure (HF) decompensation, arrhythmia, and death due to any of these events.^{7–10} Notably, there is a strong physiological link between acute exacerbations of COPD (AECOPDs) and cardiovascular events, with several shared risk factors.^{9,11} Though not fully understood, potential mechanisms include systemic inflammation, hyperinflation, and hypoxemia.^{9,11} Consequently, patients experiencing AECOPDs have elevated cardiopulmonary risk, resulting in increased risk of mortality and cardiovascular events.¹² The risk of cardiovascular events (ie, acute coronary syndrome, arrhythmia, HF, and cerebral ischemia) increases sharply after AECOPDs, particularly in the first week, and remains elevated for up to 12 months.¹³ Furthermore, the risk of death increases with the occurrence and severity of exacerbations, with one or more severe AECOPDs at baseline (defined as the first year post COPD diagnosis) associated with an 80% increased risk of death across a decade of follow-up.¹² It is important to note that cardiovascular events, and their subsequent risk, are not limited to patients with severe COPD.¹⁴ It has been reported that patients with mild to moderate airflow obstruction (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages I and II COPD) were more likely to die from cardiovascular causes than respiratory causes.¹⁴

The National Institute for Health and Care Excellence (NICE) defines AECOPDs as a sustained worsening of the patient's symptoms from their usual stable state beyond normal day-to-day variations that is acute in onset. These events are associated with worsening breathlessness, cough, increased sputum production, and change in sputum color, and are classified by NICE as mild, moderate, or severe, depending on the need for treatment and hospital admission.¹⁵ NICE and GOLD (2025 Report) provide guidance for the management of AECOPDs;^{15,16} however, established management guidelines to specifically address cardiopulmonary risk in COPD are absent.^{9,11,17,18} NHS England targets improvements in preventable respiratory-related mortality and admissions, although cardiopulmonary risk recommendations are not currently included.¹⁹

We aimed to evaluate existing information on cardiopulmonary risk and events through a literature review, and to develop consensus statements that address cardiopulmonary risk in patients with COPD. We employed a systematic literature review (SLR) to provide rigor, and to ensure transparency and reproducibility. A modified Delphi approach was used to efficiently generate and revise statements reflecting the perspectives of a multidisciplinary group and to assess whether there was consensus among the group.

In the absence of established approaches to address cardiopulmonary risk in people with COPD, the objectives for the consensus program were: to provide expert UK consensus statements and accompanying actions relating to its clinical relevance, importance, and management; and to develop a clinical pathway framework for its identification and management.

Methods

The consensus program included a review to synthesize published evidence regarding cardiopulmonary risk in patients with COPD in the UK. A modified Delphi approach was adopted to produce consensus statements based on scientific evidence and expert clinical experiences and opinion, with the aim of addressing cardiopulmonary risk in COPD.

Taskforce Members and Program Initiation

In November 2023, a multidisciplinary Taskforce of 11 respiratory and cardiology specialist healthcare professionals (HCPs) convened to identify fundamental clinical questions on the management of cardiopulmonary risk in patients with

COPD in the UK. The Taskforce comprised of specialists from primary and secondary care, including clinicians, pharmacists, and nurses. Taskforce members were selected for their academic and clinical interest in the relationship between AECOPDs and cardiopulmonary risk and/or events. The Taskforce met to define the scope and focus of the SLR and consensus program, including the key objectives, themes, and research questions, and to agree the specific methodologies to be employed.

Literature Review Methodology

An initial scoping search was conducted in November 2023 to identify relevant publications, keywords, and Medical Subject Headings (MeSH). Following this, a search of PubMed was undertaken in January 2024 to identify articles published between January 2013 and January 2024, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁰ Research questions ([Supplementary Table 1](#)) and search strings ([Supplementary Table 2](#)) were developed using the Patient, Intervention, Comparator, and Outcome (PICO) framework to address the following research questions: What is the healthcare burden of AECOPDs in the UK?; What is the link between AECOPDs and cardiopulmonary events?; How is cardiopulmonary risk currently managed in patients with COPD in the UK?; What guidelines and interventions have been implemented to optimize management of COPD in the UK?

Titles, abstracts, and, where eligibility was uncertain based on review of the abstract, full-text articles were screened against the predefined inclusion and exclusion criteria ([Supplementary Table 3](#)). As part of the abstract screening, duplications were detected by a third-party application (Rayyan.ai) and checked and removed by an analyst. The following information was extracted from the included studies: reference details; patient population; geography; study design, intervention/exposure; outcomes (ie, healthcare burden in the UK, link between AECOPDs and cardiopulmonary risk, cardiopulmonary risk management in the UK, and guidelines and interventions for COPD management optimization in the UK); and study limitations.

Consensus Program Design “Assessing Consensus”

The next phase was conducted between April 2024 and December 2024, during which a modified Delphi approach was employed to develop consensus statements relating to the four SLR research questions.²¹ This involved expert review of the information identified by the SLR, followed by the drafting of consensus statements, which were developed based on the evidence reviewed and the clinical experience of the Taskforce. The consensus statements were then subject to three rounds of review, voting, and refinement, until consensus was achieved on all key points or a lack of consensus on a topic was recognized ([Supplementary Figure 1](#)).

Round 1 Voting

After preliminary statements were drafted, consensus was sought and measured by asking the Taskforce to vote via an online survey (Microsoft Forms). This was conducted between May 3, 2024 and May 16, 2024. All statements were listed, and respondents were asked whether they “agreed”, “disagreed”, or “partially agreed, but with further amends” with the statements. Selection of “partially agreed, but with further amends” would prompt the voting member to provide comment on how the statement could be improved. The threshold for consensus was 75% of respondents voting that they “agreed” with the statements. Following voting, the results of the survey were collated and presented to the Taskforce at a virtual meeting, which allowed for discussion and confirmation of initial revisions to the statements, where required. The statements were then amended in preparation for the second round of voting.

Round 2 Voting

The second round of voting, conducted between May 29, 2024 and June 10, 2024, included two independent voting processes, in which respondents voted on their level of agreement on the amended statements. Respondents were also given the opportunity to suggest edits to the statements. Consensus was again measured among the Taskforce using a survey (Microsoft Forms). Once the Taskforce members had completed voting and consensus was measured, the statements were updated. Following these revisions, external groups were invited to participate in a round of validation

voting. Those invited to vote included UK HCPs who were invited by the Taskforce, selected members of regional and national COPD working groups, and National Respiratory Leadership Forum (NRLF) meeting delegates. The revised statements were presented via a survey and respondents were invited to vote on their level of agreement or disagreement with the statements using a 1–9 Likert scale. The ratings were: 1–3, disagree; 4–6, neither agree nor disagree; and 7–9, agree. The threshold for consensus was set at 75% of respondents giving a rating of 7–9 for a statement.

Round 3 Voting

The third round of voting also included two independent voting processes, in which respondents voted on their level of agreement with the amended statements. Again, consensus was measured using a survey (Microsoft Forms). Those invited to vote included the Taskforce, HCPs from regional and national working groups, and delegates from the NRLF, including representation from primary and secondary care (conducted between October 29, 2024 and December 18, 2024). Similarly to Round 2, respondents were invited to vote on the statements via a survey using a 1–9 Likert scale. There were 77 respondents and the threshold for consensus was set at 75% of respondents giving a rating of 7–9 for a statement.

Clinical Pathway Framework Methodology

To complement the consensus statements and support their implementation in clinical practice, a Taskforce workshop was conducted in November 2024 to formulate a clinical pathway framework to support the recognition and management of cardiopulmonary risk in patients with COPD using the consensus statements. Key factors, clinical characteristics, observations, and assessments as part of risk identification, as well as actions that could be taken to manage cardiopulmonary risk in patients with COPD, were outlined. These were categorized as either “essential” or “desirable” and developed into a Cardiopulmonary Risk Matrix (Figure 1).

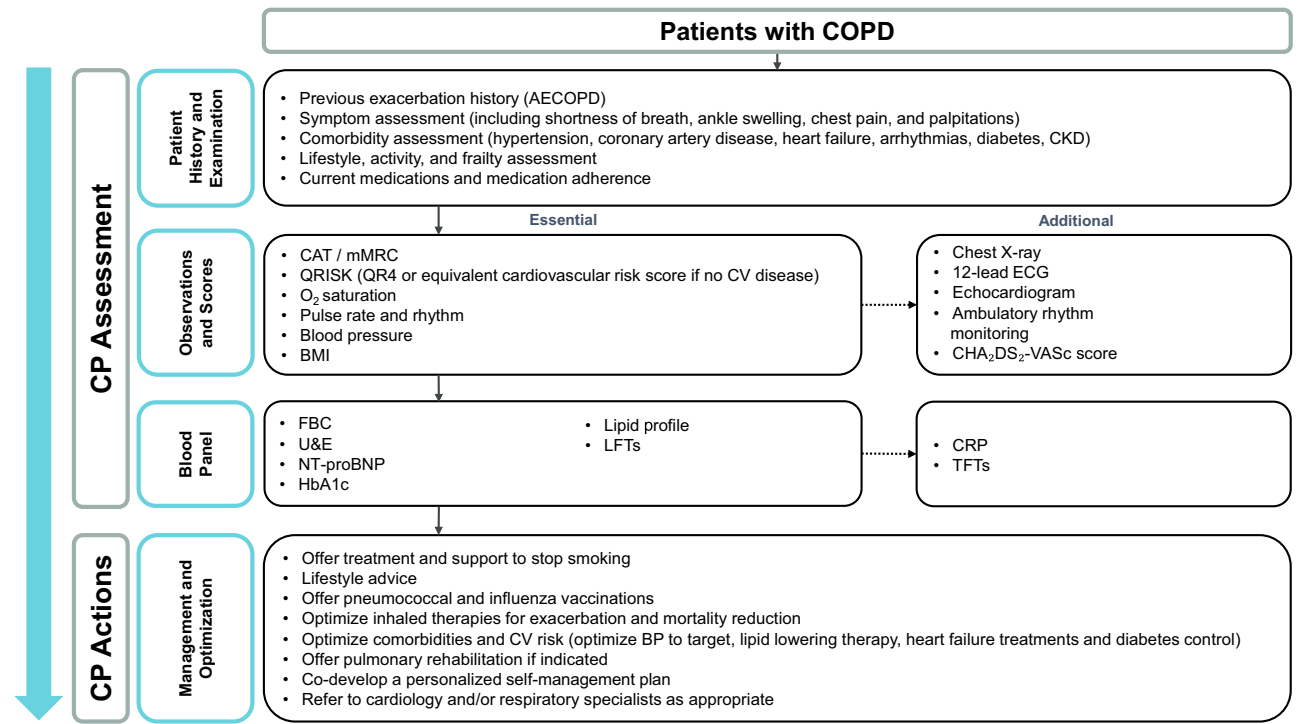


Figure 1 Cardiopulmonary Risk Matrix.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; BP, blood pressure; CAT, COPD Assessment Test; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category (stroke risk score); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CP, cardiopulmonary; CRP, C-reactive protein; ECG, electrocardiogram; FBC, full blood count; HbA1c, hemoglobin A1c; LFT, liver function test; mMRC, modified Medical Research Council dyspnea scale; NT pro-BNP, N-terminal pro b-type natriuretic peptide; QRISK, cardiovascular risk score; TFT, thyroid function test; U&E, urea and electrolytes.

Results

Literature Review

The initial publication search yielded 1649 potentially relevant publications, including 398 relevant to research question 1 and 766, 403, and 82 to clinical questions 2, 3, and 4, respectively. The removal of duplicates and publications that did not meet the inclusion criteria left 57 unique publications relevant for question 1; 124 for clinical question 2; 13 for clinical question 3; and two for clinical question 4. PRISMA diagrams detailing the full screening process can be found in [Supplementary Figures 2–5](#).

Clinical Question 1. Burden of Acute Exacerbations of COPD: What is the Healthcare Burden of Acute Exacerbations of COPD in the UK?

Fifty-seven publications met the inclusion criteria for examining the healthcare burden of AECOPDs in the UK.^{12,18,22–74} Most of the studies reported were observational (68%), with randomized controlled trials, interventional studies, prognostic tool design, online surveys, case studies, meta-analyses and SLRs, and model analyses also being included. Most studies examined primary care data (54%) and used the Clinical Practice Research Datalink (CPRD) database, while some linked those data with those available in the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases to obtain secondary care and sociodemographic data.

Incidence rates of AECOPDs were reported across several studies, with variation in rates observed. One observational study analyzed data from 340,515 primary and secondary care COPD-patient records, finding that 46.8% of patients had at least one moderate exacerbation during a 15-year follow-up period.⁷² Another primary care observational study analyzed 8282 records and retrospectively reported that 45.4% of patients experienced at least one AECOPD during the 12 months prior to study enrollment.⁶⁰ A primary care study (N=315,184) reported the rate of exacerbations experienced in the follow-up period between 19.3 and 66.6 events/100 person-years.⁷¹

Of 21 publications that investigated mortality, seven found that patients experiencing AECOPDs were at increased risk of mortality compared with patients with stable COPD, with mortality risk being most highly elevated for those experiencing frequent AECOPDs.^{12,25,29,43,70,72,75} Study populations, duration, and how mortality was measured varied across the included studies. A large primary care study including data from 67,516 patients over 14 years demonstrated all-cause mortality, during a mean follow-up period of 4 years, of 28.3% in patients experiencing any AECOPD compared with 22.3% in those not experiencing an AECOPD.⁴³ Another cohort study analyzing 10 years of data reported the effect of AECOPDs in 99,574 patients. In comparison with patients who did not experience an AECOPD during the first year of the study period, those with two or more moderate AECOPD events during the first year were associated with an increased risk of mortality (hazard ratio [HR]: 1.10; 95% confidence interval [CI] 1.03, 1.18).¹²

Six publications provided data for quality of life measurements, indicating that COPD negatively impacts quality of life.^{18,22,29,30,45,66} An online survey found that 27.1% of patients reported unemployment due to their COPD and 17.6% reported fear of exacerbations hindering their ability to get up in the morning.¹⁸

Healthcare burden was identified in 31 publications, and though hospital length of stay varied, likely due to varying study populations and comorbidities considered, patients experiencing AECOPDs had frequent contacts with healthcare providers leading to increased costs.^{18,23,24,28–30,32,33,35–37,39,42,46–48,50,53,56,59,61,62,66,68,69,73–76} A multicenter, retrospective observational study assessing 3 years of primary care data from 511 patients with COPD found that those patients experiencing frequent AECOPDs (≥ 3 exacerbations per year) had a median (interquartile range) of 6.67 (5.33–8.67) primary care contacts per year and 1.0 (0.33–2.67) secondary care contacts per year; 21% were hospitalized for COPD each year.⁶⁶ In contrast, patients experiencing no AECOPD had a median of 1.33 (0.67–2.00) primary care contacts per year and no secondary care contacts; 1% were hospitalized for COPD each year.⁶⁶ Additionally, a large (N=58,589) cohort analysis of UK hospitalizations over 12 months found that the costs of managing exacerbations increased with their frequency, with the majority of COPD-related costs attributable to primary care interactions.⁵⁶ The annual cost of managing patients experiencing two or more exacerbations categorized in stage 4 of GOLD airflow obstruction was £871.16, excluding medications, based on 2010–2011 National Health Service (NHS) reference costs.⁵⁶

Clinical Question 2. What is the Link Between Acute Exacerbations of COPD and Cardiopulmonary Events?

A total of 124 publications were included in the final review.^{5,29,33,43,52,63,71–73,77–190} A large proportion (59%) occurred in, or utilized data from, secondary care. Most studies (84%) were observational but relevant case studies, database analyses, systematic reviews, and randomized controlled trials were also identified. The publications covered 35 countries in total, with most reporting studies conducted in the USA, China, the UK, and Europe. Overall, patients experiencing AECOPDs were found to be at high risk of major adverse cardiovascular events (MACE), including MI, stroke, and cardiovascular-related mortality.^{124,139,153}

A meta-analysis of observational studies found an increased risk of MACE in the 1–3 months after an AECOPD compared with no occurrence of AECOPD, reporting a relative risk (RR) of 2.43 (95% CI: 1.40, 4.20) for acute MI and an RR of 1.68 (95% CI: 1.19, 2.38) for stroke.¹³⁹ One publication analyzing the records of 25,764 patients from a UK COPD database, found no association between the frequency of exacerbations and stroke risk (odds ratio [OR] 0.95: 95% CI: 0.89, 1.01).¹⁸³

A large (N=67,516) open-cohort study compared cause-specific mortality rates for up to 14 years and adjusted for a number of risk factors, including sex, socioeconomic status, smoking status, body mass index, GOLD stage, and comorbidities.⁴³ The study found respiratory-related deaths were more frequent in patients experiencing AECOPDs (40.3%) compared with non-exacerbators (29.2%).⁴³ Conversely, CVD-related deaths were slightly more common in non-exacerbators (26.2%) compared with those experiencing AECOPDs (22.9%), possibly because of under-recognition (and consequent under-treatment) of comorbidities in non-exacerbators due to fewer healthcare contacts and hospitalizations where CVD diagnoses could be made.⁴³ Furthermore, a large health registry study including data for 340,515 patients found that those with a history of frequent and severe exacerbations at baseline were more likely to experience higher rates of future exacerbations over an average follow-up of 5.3 years, compared with patients with a history of infrequent or less severe exacerbations.⁷² The study identified a correlation between baseline severity and future severity of exacerbations, as well as between baseline frequency and future frequency of exacerbations.⁷²

Clinical Question 3. How is Cardiopulmonary Risk Currently Managed in Patients with COPD in the UK?

Thirteen of the publications included in the review examined the management of cardiopulmonary risk in the UK.^{33,51,114,183,191–200} Most of the publications were observational studies (69%), with the remainder including interventional and prognostic tool design studies. The majority (70%) were large scale, utilizing databases across England or the UK, while four were smaller, single-center studies. There was heterogeneity in study populations, with notable variation in COPD definitions, population age, and comorbidities considered. Ten publications reported concurrent cardiopulmonary events in patients with COPD, but none evaluated the effectiveness or importance of managing the risk of such events.^{33,183,191–194,196–198}

Many studies examined cardiovascular risk in patients with COPD but none evaluated the impact of cardiovascular treatment on COPD outcomes or cardiopulmonary risk management. For example, two studies derived and assessed prognostic tools to evaluate the mortality risk in patients with COPD and AECOPD.^{32,193} Although each of these scores evaluated the risk of cardiovascular comorbidities in patients with COPD, neither discussed the concept or management of cardiopulmonary risk.^{32,193}

Clinical Question 4. What Policy Changes are in Place to Optimize Management of COPD in the UK?

Two relevant guidelines detailing the optimal management of patients experiencing AECOPDs in the UK were identified.²⁰¹ The British Thoracic Society (BTS) 2020 guidelines evaluated evidence supporting the use of long-term, low-dose macrolide therapy for adult respiratory diseases and for reducing rates of AECOPDs. One “good practice point” suggested the optimization of pharmacological and non-pharmacological interventions prior to considering long-term treatment with macrolides, such as smoking cessation, optimized inhaler technique, optimized self-management care plans, airway clearance techniques, and attendance at pulmonary rehabilitation courses. These recommendations were not specifically to address cardiopulmonary risk reduction, which was not discussed in the guideline.²⁰¹ The NICE 2019 guidance offered recommendations for the management of AECOPDs through systemic corticosteroids and bronchodilators, alongside supportive measures like oxygen therapy and non-invasive ventilation, where required.

Cardiopulmonary risk management was not mentioned; however, additional cardiac investigations (eg, electrocardiogram and serum natriuretic peptides) were recommended if CVD or pulmonary hypertension was suspected. An echocardiogram was also recommended if these conditions are suspected, as well as if clinical signs of cardiac or respiratory distress are present (eg, tachycardia, oedema, cyanosis, or features of cor pulmonale).¹⁵ The GOLD Report for 2025 includes recommendations based on CVD risk in patients experiencing AECOPDs but was not included in the SLR because it is not UK specific and was published after this SLR.¹⁶

Consensus Program

Consensus Statements

A preliminary set of statements was drafted and subjected to voting and revision. Following refinement, and consolidation to avoid redundancy, a total of 18 statements were included in the final round of voting and all reached the consensus threshold (Table 1). The statements are divided into four categories: burden of AECOPDs within the UK; the link between AECOPDs and cardiopulmonary events; the management of cardiopulmonary risk in the UK; and guidelines for the management of cardiopulmonary risk. Nine statements reflect the current situation, and nine statements are recommended actions that offer potential benefits.

In the third round of voting, each statement met the requirement for consensus (>75% respondents giving a rating of 7–9 for a statement). There was 100% consensus among the Taskforce members for all statements (Table 1).

Table 1 Consensus Statements

Consensus Statements	Score (Mean)	Consensus (ie, Votes Between 7–9) (%)
Healthcare burden of AECOPDs in the UK		
Approximately half of patients with known COPD experience AECOPDs in the UK. AECOPDs are associated with increased cardiopulmonary risk, further AECOPDs, and mortality.	8.4	95%
Action: Proactive detection of risk factors and intervention is required to prevent AECOPDs and reduce the risk of cardiopulmonary events.	8.4	95%
Patients who experience AECOPDs have higher healthcare resource utilization than patients who do not experience AECOPDs, including high hospitalization and readmission rates.	8.7	99%
Multiple factors contribute to the direct and indirect costs of managing AECOPDs including, but not limited to, COPD disease severity, long-term conditions, AECOPD frequency, general health, medications use, and healthcare resource utilization.	8.6	100%
Action: Optimizing COPD management through preventing AECOPDs may help address the overall cost of managing COPD.	8.4	96%
The link between AECOPDs and cardiopulmonary events		
Patients experiencing AECOPDs are at increased risk of cardiopulmonary events, including MI, stroke, HF, arrhythmia, and respiratory or cardiovascular death.	8.5	98%
Action: Preventing AECOPDs is important for improving cardiopulmonary outcomes, and helping prevent premature mortality.	8.4	95%
The relationship between cardiopulmonary events and AECOPDs may be bidirectional, with cardiac events such as HF and MI potentially increasing the risk of future AECOPDs, hospitalization, and readmission, and vice versa.	7.8	86%
Action: Improving management of cardiovascular disease in patients with COPD is likely to improve clinical outcomes.	8.4	96%
An AECOPD may initiate functional decline in patients with COPD.	8.6	98%
Action: Preventing AECOPDs is important in limiting functional decline.	8.6	97%

(Continued)

Table 1 (Continued).

Consensus Statements	Score (Mean)	Consensus (ie, Votes Between 7–9) (%)
Cardiopulmonary risk management in the UK		
Cardiopulmonary risk is under-recognized and sub-optimally managed in patients with COPD.	8.4	97%
In patients with concomitant COPD and cardiovascular disease, current management strategies are typically not integrated between specialties and/or between primary and secondary care.	8.4	100%
Action: An integrated clinical approach for patients with concomitant COPD and cardiovascular disease could provide personalized treatment to improve outcomes.	8.3	95%
Guidelines and interventions for management in the UK		
Incorporation of patient-centered cardiopulmonary risk management into routine care in patients with COPD is currently limited in the UK.	8.0	95%
Action: Addressing cardiopulmonary risk has the potential to improve care and outcomes in patients with COPD.	8.4	95%
Action: Decision-support tools and protocols may help estimate cardiopulmonary risk in patients with COPD, supporting optimal management.	8.2	92%
Action: Policy, research, and clinical approaches should be designed to reduce cardiopulmonary events in patients with COPD.	8.4	94%

Abbreviations: AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; HF, heart failure; MI, myocardial infarction.

Cardiopulmonary Risk Matrix

A Cardiopulmonary Risk Matrix was developed (Figure 1) to provide a clinical pathway framework for those involved in the care of patients with COPD, outlining key assessments and subsequent actions.

Discussion

We conducted an SLR of relevant studies, developed consensus statements using a modified Delphi approach, and established recommended or key actions along with a Cardiopulmonary Risk Matrix. This report identified a significant healthcare burden of AECOPDs within the UK.^{12,18,25,29,36,43–45,54,56,66,72,197} Patients experiencing AECOPDs had higher risk of mortality and MACE, reduced quality of life, and more contacts with HCPs, compared with those who did not exacerbate.^{18,22,29,30,33,43,45,66,70,72,75} Despite these associations, and an increase in management costs with AECOPD frequency, current UK guidelines lack specificity regarding addressing cardiopulmonary risk.^{33,36,66,183,191–194,196–198} Only two relevant guidelines discussed AECOPD treatment, with the management of cardiovascular risk only covered in NICE guidelines.^{15,201} In these, cardiac investigations were recommended if there was clinical suspicion of CVD in patients with COPD, but details about when and how best to investigate for CVD were lacking.^{15,201} The increased risk of cardiovascular events following AECOPDs and consequent increased long-term risk for both respiratory and cardiovascular-related mortality has been highlighted by the recent international GOLD 2025 Report.¹⁶ Both NICE and GOLD emphasize the importance of early recognition and provide guidance for the optimized management of AECOPDs.^{15,16} From a CVD perspective, the latest QRISK4 score (QR4) includes COPD as a risk factor, and has shown that COPD is associated with MACE independent of CVD risk factors.²⁰² QR4 can, in turn, be used to evaluate cardiovascular risk in patients experiencing AECOPDs, as outlined in the Cardiopulmonary Risk Matrix (Figure 1). Our matrix was developed to provide HCPs with a framework for incorporating cardiopulmonary risk assessments and management into routine clinical practice.

AECOPDs are key drivers of cardiopulmonary events, though the relationship may be bidirectional, with cardiovascular events also increasing the risk of future AECOPDs.^{124,139,153} Correct identification of AECOPDs and cardiovascular risk is therefore important for cardiopulmonary management, but few studies provided suggestions for the identification of cardiopulmonary risk.^{9,17} A recent review by Jones, et al, suggested substantial under-reporting of AECOPDs by patients to HCPs, hindering the management and prevention of future AECOPDs.²⁰³ In the SLR reported

here, several studies discussed the potentially under-recognized burden of AECOPDs, particularly in those patients managing their COPD at home, as well as undiagnosed comorbidities.^{66,182} Further supporting this trend, the COPD cohort of the COSYCONET study found that a large proportion of patients with suspicious echocardiography findings did not have a diagnosis or treatment for CVD.²⁰⁴ COPD and CVD were often treated independently, highlighting the gap in integrated care approaches.¹⁹⁷

Direct and indirect costs of managing AECOPDs and subsequent cardiovascular events could be reduced by treatment optimization, which has been shown to reduce the number of AECOPDs and associated admissions and length of stay.^{26,62} In addition to financial costs, impacts of AECOPDs include reduced quality of life, declining mental health, carer burden, increased breathlessness, and functional decline. These factors contribute to increased risk of falls, and place a strain on carers and healthcare systems.^{205,206} Of note, there are few NHS commissioning frameworks or financial incentives specifically targeting cardiopulmonary risk, with the current focus being on early diagnosis of COPD, pulmonary rehabilitation, and efficiencies.^{207,208} Inclusion of integrated cardiopulmonary strategies could help to align funding with service needs.^{207,208}

The gap in managing cardiopulmonary risk in patients experiencing AECOPDs suggests there is an opportunity to optimize care and reduce the cost of COPD management through the development of new UK policies and clinical guidance.

Clinical Implications

There is a need for multidisciplinary integrated care models including all HCPs involved in managing patients with COPD to identify and manage cardiopulmonary risk, and the Cardiopulmonary Risk Matrix/assessment tool proposed in this review could be a step towards achieving this. The Cardiopulmonary Risk Matrix could be referred to around the time of an AECOPD and/or as part of regular patient follow-up to identify and optimize cardiopulmonary risk in patients with COPD. Further education and training on cardiopulmonary risk identification and management is required to ensure it is prioritized by care systems. Additionally, COPD hospital care bundles should provide guidance on CVD assessment of both atherosclerotic CVD and HF.

Policy Implications

More funding for the development of cardiopulmonary research and guidelines is required in order to allow collection of data for large-scale registries of patients in primary and secondary care, with COPD and comorbid CVD, which in turn could inform future policies. Contract enablers should also be put in place at a national level, such as a framework of cardiopulmonary health outcome indicators for use in managing patients experiencing AECOPDs, which is something this review has highlighted is lacking in current practice.

Strengths and Limitations

The SLR was carried out according to PRISMA guidance to ensure transparency and reproducibility. Evidence was summarized and gaps in the literature were identified to help guide future research. The consensus statements were developed by the Taskforce, and consensus was gained from the group as well as externally validated by a wider group of UK HCPs. This validation process not only strengthens the consensus statements but also ensures they are practical, relevant, and applicable across diverse clinical settings, supporting their adoption in real-world practice. Unintentional bias in selection of Taskforce members cannot be ruled out; however, any potential impacts will have been mitigated by involving the wider group.

A limitation of this review was the heterogeneity of studies included, with a variety of study types, and patient populations included, making interpretation of the whole body of evidence challenging. Additionally, as many included publications reported retrospective cohort studies, database analyses, SLRs, observational studies, or cases reports, there may be variation in the classification of AECOPD severity. Few of the included interventional studies were randomized controlled trials. Another limitation is the complexity of cardiopulmonary risk in this patient population, including the bidirectional nature of MACE and AECOPDs, which makes interplay difficult to synthesize from the current evidence. Generally, consensus statements reflecting the current situation are based primarily on evidence identified through the

SLR and on clinical experience, whereas those recommending action rely, to a greater extent, on opinion and interpretation of available information.

Conclusion

Patients with COPD are at risk of cardiopulmonary events and associated mortality and morbidity. While cardiopulmonary risk is widely reported in the UK, there has been limited guidance on management of that risk in terms of respiratory and cardiac care, especially for those experiencing AECOPDs. This consensus program highlights an opportunity and establishes a foundation for future interdisciplinary research and guidelines to address these critical needs.

Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; BP, blood pressure; BTS, British Thoracic Society; CAT, COPD assessment test; CI, confidence interval; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category (stroke risk score); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CP, cardiopulmonary; CPRD, Clinical Practice Research Datalink; CRP, C-reactive protein; CVD, cardiovascular disease; ECG, electrocardiogram; FBC, full blood count; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HbA1c, hemoglobin A1c; HCP, healthcare professional; HES, Hospital Episode Statistics; HF, heart failure; HR, hazard ratio; LFT, liver function test; MeSH, Medical Subject Headings; MI, myocardial infarction; mMRC, modified Medical Research Council dyspnea scale; NT pro-BNP, N-terminal pro b-type natriuretic peptide; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NRLF, National Respiratory Leadership Forum; ONS, Office for National Statistics; OR, odds ratio; PICO, Patient, Intervention, Comparator, and Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QRISK, cardiovascular risk score; RR, relative risk; SLR, systematic literature review; TFT, thyroid function test; U&E, urea and electrolytes; UK, United Kingdom.

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References

- Office for National Statistics. Death registration summary statistics, England, and Wales: 2022. 2023. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/deathregistrationsummarystatisticsenglandandwales/2022>. Accessed November 18, 2024.
- Snell N, Strachan D, Hubbard R, Gibson J, Gruffydd-Jones K, Jarrold I. S32 Epidemiology of chronic obstructive pulmonary disease (COPD) in the uk: findings from the British lung foundation's 'respiratory health of the nation' project. *Thorax*. 2016;71(Suppl 3):A20. doi:10.1136/thoraxjnl-2016-209333.38
- GOV.UK. Office for Health Improvement and Disparities. Official Statistics. INteractive Health Atlas of Lung conditions in England: INHALE: March 2023 Update. 2023. Available from: <https://www.gov.uk/government/statistics/interactive-health-atlas-of-lung-conditions-in-england-inhale-march-2023-update>. Accessed October 23, 2024.
- National Institute for Health and Care Excellence. Briefing paper. Chronic obstructive pulmonary disease (COPD) update. 2015. Available from: <https://www.nice.org.uk/guidance/qs10/documents/briefing-paper>. Accessed October 29, 2024.
- Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J*. 2006;28(6):1245–1257. doi:10.1183/09031936.00133805
- Miller J, Edwards LD, Agusti A, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir Med*. 2013;107(9):1376–1384. doi:10.1016/j.rmed.2013.05.001
- Hurst JR, Gale CP, Global Working Group on Cardiopulmonary Risk. MACE in COPD: addressing cardiopulmonary risk. *Lancet Respir Med*. 2024;12(5):345–348. doi:10.1016/S2213-2600(24)00038-9
- Gale CP, Berg DD, Bhutani M; on behalf of the Global Working Group on Cardiopulmonary Risk. The global working group on cardiopulmonary risk in chronic obstructive pulmonary disease. *EHJ*. 2024;45(44):4676–4678. doi:10.1093/eurheartj/ehae628
- Singh D, Han MK, Hawkins NM, et al. Implications of cardiopulmonary risk for the management of COPD: a narrative review. *Adv Ther*. 2024;41(6):2151–2167. doi:10.1007/s12325-024-02855-4
- Gale CP, Hurst JR, Hawkins NM, et al. Identification and management of cardiopulmonary risk in patients with COPD: a multidisciplinary consensus and modified Delphi study. *Eur J Prev Cardiol*. 2025;zwaf119. PMID: 40037333. doi:10.1093/eurjpc/zwaf119
- Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev*. 2018;27(149):180057. doi:10.1183/16000617.0057-2018
- Rothnie KJ, Mullerova H, Smeeth L, Quint JK. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198(4):464–471. doi:10.1164/rccm.201710-2029OC
- Swart KMA, Baak BN, Lemmens L, et al. Risk of cardiovascular events after an exacerbation of chronic obstructive pulmonary disease: results from the EXACOS-CV cohort study using the PHARMO Data Network in the Netherlands. *Respir Res*. 2023;24(1):293. doi:10.1186/s12931-023-02601-4
- Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med*. 2006;100(1):115–122. doi:10.1016/j.rmed.2005.03.035
- National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management (NG115). 2019. Available from: <https://www.nice.org.uk/guidance/NG115>. Accessed November 14, 2024.
- Global strategy for prevention, diagnosis and management of COPD (GOLD). 2025 GOLD report. 2025. Available from: <https://goldcopd.org/2025-gold-report/>. Accessed 14, November 2024.
- Shrikrishna D, Taylor CJ, Stonham C, Gale CP. Exacerbating the burden of cardiovascular disease: how can we address cardiopulmonary risk in individuals with chronic obstructive pulmonary disease? *Eur Heart J*. 2024;45(4):247–249. doi:10.1093/eurheartj/ehad669
- Titmarsh S, Poliziani M, Russell RE. "Breathing New Life Into Chronic Obstructive Pulmonary Disease (COPD)" - results from an online survey of UK patients. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2799–2807. doi:10.2147/COPD.S222139
- NHS England. Quality and Outcomes Framework Guidance for 2024/25. 2024. Available from: <https://www.england.nhs.uk/wp-content/uploads/2024/03/PRN01104-Quality-and-outcomes-framework-guidance-for-2024-25.pdf>. Accessed January 7, 2025.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
- Savic LC, Smith AF. How to conduct a Delphi consensus process. *Anaesthesia*. 2023;78(2):247–250. doi:10.1111/anae.15808
- Acidinium for COPD? *Drug Ther Bull*. 2013;51(4):45–48. doi:10.1136/dtb.2013.4.0175
- Bafadhel M, Greening NJ, Harvey-Dunstan TC, et al. Blood eosinophils and outcomes in severe hospitalized exacerbations of COPD. *Chest*. 2016;150(2):320–328. doi:10.1016/j.chest.2016.01.026

24. Bakerly ND, Browning D, Boucot I, et al. The impact of fluticasone furoate/vilanterol on healthcare resource utilisation in the Salford Lung Study in chronic obstructive pulmonary disease. *Ther Adv Respir Dis*. 2021;15:17534666211001013. doi:10.1177/17534666211001013
25. Boggon R, Hubbard R, Smeeth L, et al. Variability of antibiotic prescribing in patients with chronic obstructive pulmonary disease exacerbations: a cohort study. *BMC Pulm Med*. 2013;13:32. doi:10.1186/1471-2466-13-32
26. Capstick TG, Azeez NF, Deakin G, Goddard A, Goddard D, Clifton IJ. Ward based inhaler technique service reduces exacerbations of asthma and COPD. *Respir Med*. 2021;187:106583. doi:10.1016/j.rmed.2021.106583
27. Crooks MG, den Brinker A, Hayman Y, et al. Continuous cough monitoring using ambient sound recording during convalescence from a COPD exacerbation. *Lung*. 2017;195(3):289–294. doi:10.1007/s00408-017-9996-2
28. Devereux G, Cotton S, Fielding S, et al. Effect of theophylline as adjunct to inhaled corticosteroids on exacerbations in patients with COPD: a randomized clinical trial. *JAMA*. 2018;320(15):1548–1559. doi:10.1001/jama.2018.14432
29. Devereux G, Cotton S, Fielding S, et al. Low-dose oral theophylline combined with inhaled corticosteroids for people with chronic obstructive pulmonary disease and high risk of exacerbations: a RCT. *Health Technol Assess*. 2019;23(37):1–146. doi:10.3310/hta23370
30. Echevarria C, Gray J, Hartley T, et al. Home treatment of COPD exacerbation selected by DECAF score: a non-inferiority, randomised controlled trial and economic evaluation. *Thorax*. 2018;73(8):713–722. doi:10.1136/thoraxjnl-2017-211197
31. Echevarria C, Steer J, Bourke SC. Comparison of early warning scores in patients with COPD exacerbation: DECAF and NEWS score. *Thorax*. 2019;74(10):941–946. doi:10.1136/thoraxjnl-2019-213470
32. Echevarria C, Steer J, Heslop-Marshall K, et al. Validation of the DECAF score to predict hospital mortality in acute exacerbations of COPD. *Thorax*. 2016;71(2):133–140. doi:10.1136/thoraxjnl-2015-207775
33. Echevarria C, Steer J, Heslop-Marshall K, et al. The PEARL score predicts 90-day readmission or death after hospitalisation for acute exacerbation of COPD. *Thorax*. 2017;72(8):686–693. doi:10.1136/thoraxjnl-2016-209298
34. Echevarria C, Steer J, Wason J, Bourke S. Oxygen therapy and inpatient mortality in COPD exacerbation. *Emerg Med J*. 2021;38(3):170–177. doi:10.1136/emered-2019-209257
35. Fermont JM, Bolton CE, Fisk M, et al. Risk assessment for hospital admission in patients with COPD; a multi-centre UK prospective observational study. *PLoS One*. 2020;15(2):e0228940. doi:10.1371/journal.pone.0228940
36. Foo J, Landis SH, Maskell J, et al. Continuing to confront COPD international patient survey: economic Impact of COPD in 12 countries. *PLoS One*. 2016;11(4):e0152618. doi:10.1371/journal.pone.0152618
37. Harrison MT, Short P, Williamson PA, Singanayagam A, Chalmers JD, Schembri S. Thrombocytosis is associated with increased short and long term mortality after exacerbation of chronic obstructive pulmonary disease: a role for antiplatelet therapy? *Thorax*. 2014;69(7):609–615. doi:10.1136/thoraxjnl-2013-203996
38. James GD, Petersen I, Nazareth I, Wedzicha JA, Donaldson GC. Use of long-term antibiotic treatment in COPD patients in the UK: a retrospective cohort study. *NPJ Prim Care Respir Med*. 2013;22(3):271–277. doi:10.4104/pcrj.2013.00061
39. Johnson-Warrington V, Rees K, Gelder C, Morgan MD, Singh SJ. Can a supported self-management program for COPD upon hospital discharge reduce readmissions? A randomized controlled trial. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1161–1169. doi:10.2147/COPD.S91253
40. Jones R, Martin J, Thomas V, et al. The comparative effectiveness of initiating fluticasone/salmeterol combination therapy via pMDI versus DPI in reducing exacerbations and treatment escalation in COPD: a UK database study. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2445–2454. doi:10.2147/COPD.S141409
41. Kerkhof M, Voorham J, Dorinsky P, et al. The long-term burden of COPD exacerbations during maintenance therapy and lung function decline. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1909–1918. doi:10.2147/COPD.S253812
42. Landis SH, Wurst K, Le HV, Bonar K, Puneekar YS. Can assessment of disease burden prior to changes in initial COPD maintenance treatment provide insight into remaining unmet needs? A retrospective database study in UK primary care. *COPD*. 2017;14(1):80–85. doi:10.1080/15412555.2016.1240159
43. Lenoir A, Whittaker H, Gayle A, Jarvis D, Quint JK. Mortality in non-exacerbating COPD: a longitudinal analysis of UK primary care data. *Thorax*. 2023;78(9):904–911. doi:10.1136/thorax-2022-218724
44. Mandal S, Howes TQ, Parker M, Roberts CM. The use of a prospective audit proforma to improve door-to-mask times for acute exacerbations chronic obstructive pulmonary disease (COPD) requiring non-invasive ventilation (NIV). *COPD*. 2014;11(6):645–651. doi:10.3109/15412555.2014.898044
45. Mi E, Mi E, Ewing G, et al. Associations between the psychological health of patients and carers in advanced COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2813–2821. doi:10.2147/COPD.S139188
46. Moore E, Newson R, Joshi M, et al. Effects of pulmonary rehabilitation on exacerbation number and severity in people with COPD: an historical cohort study using electronic health records. *Chest*. 2017;152(6):1188–1202. doi:10.1016/j.chest.2017.05.006
47. Morton K, MacNeill S, Sanderson E, et al. Evaluation of 'care bundles' for patients with chronic obstructive pulmonary disease (COPD): a multisite study in the UK. *BMJ Open Respir Res*. 2019;6(1):e000425. doi:10.1136/bmjresp-2019-000425
48. Mullerova H, Meeraus WH, Galkin DV, Albers FC, Landis SH. Clinical burden of illness among patients with severe eosinophilic COPD. *Int J Chron Obstruct Pulmon Dis*. 2019;14:741–755. doi:10.2147/COPD.S194511
49. Naqvi M, Khachi H. The barriers to accessing primary care resulting in hospital presentation for exacerbation of asthma or chronic obstructive pulmonary disease in a large teaching hospital in London. *Respir Med*. 2016;117:162–165. doi:10.1016/j.rmed.2016.05.020
50. Oshagbemi OA, Franssen FME, Braeken DCW, et al. Blood eosinophilia, use of inhaled corticosteroids, and risk of COPD exacerbations and mortality. *Pharmacoepidemiol Drug Saf*. 2018;27(11):1191–1199. doi:10.1002/pds.4655
51. Oshagbemi OA, Franssen FME, Wouters EFM, et al. C-reactive protein as a biomarker of response to inhaled corticosteroids among patients with COPD. *Pulm Pharmacol Ther*. 2020;60:101870. doi:10.1016/j.pupt.2019.101870
52. Pikoula M, Quint JK, Nissen F, Hemingway H, Smeeth L, Denaxas S. Identifying clinically important COPD sub-types using data-driven approaches in primary care population based electronic health records. *BMC Med Inform Decis Mak*. 2019;19(1):86. doi:10.1186/s12911-019-0805-0

53. Price D, Asukai Y, Ananthapavan J, Malcolm B, Radwan A, Keyzor I. A UK-based cost-utility analysis of indacaterol, a once-daily maintenance bronchodilator for patients with COPD, using real world evidence on resource use. *Appl Health Econ Health Policy*. 2013;11(3):259–274. doi:10.1007/s40258-013-0021-5
54. Punekar YS, Landis SH, Wurst K, Le H. Characteristics, disease burden and costs of COPD patients in the two years following initiation of long-acting bronchodilators in UK primary care. *Respir Res*. 2015;16:141. doi:10.1186/s12931-015-0295-2
55. Punekar YS, Naya I, Small M, et al. Bronchodilator reliever use and its association with the economic and humanistic burden of COPD: a propensity-matched study. *J Med Econ*. 2017;20(1):28–36. doi:10.1080/13696998.2016.1223085
56. Punekar YS, Shukla A, Mullerova H. COPD management costs according to the frequency of COPD exacerbations in UK primary care. *Int J Chron Obstruct Pulmon Dis*. 2014;9:65–73. doi:10.2147/COPD.S54417
57. Punekar YS, Wurst K, Shukla A. Resource use and costs up to two years post diagnosis among newly diagnosed COPD patients in the UK primary care setting: a retrospective cohort study. *COPD*. 2015;12(3):267–275. doi:10.3109/15412555.2014.933953
58. Ramakrishnan S, Jeffers H, Langford-Wiley B, et al. Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): a non-inferiority, multicentre, double-blind, placebo-controlled, randomised controlled trial. *Lancet Respir Med*. 2024;12(1):67–77. doi:10.1016/S2213-2600(23)00298-9
59. Russell R, Beer S, Pavord ID, Pullinger R, Bafadhel M. The acute wheezy adult with airways disease in the emergency department: a retrospective case-note review of exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis*. 2019;14:971–977. doi:10.2147/COPD.S190085
60. Sansbury LB, Lipson DA, Bains C, Anley GA, Rothnie KJ, Ismaila AS. Disease burden and healthcare utilization among patients with chronic obstructive pulmonary disease (COPD) in England. *Int J Chron Obstruct Pulmon Dis*. 2022;17:415–426. doi:10.2147/COPD.S336158
61. Sansbury LB, Rothnie KJ, Bains C, Compton C, Anley G, Ismaila AS. Healthcare, medication utilization and outcomes of patients with COPD by GOLD classification in England. *Int J Chron Obstruct Pulmon Dis*. 2021;16:2591–2604. doi:10.2147/COPD.S318969
62. Sansbury LB, Wood RP, Anley GA, Nam Y, Ismaila AS. Quantifying the economic impact of delayed multiple-inhaler triple therapy initiation in patients with COPD: a retrospective cohort study of linked electronic medical record and hospital administrative data in England. *Int J Chron Obstruct Pulmon Dis*. 2021;16:2795–2808. doi:10.2147/COPD.S312853
63. Schembri S, Williamson PA, Short PM, et al. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ*. 2013;346:f1235. doi:10.1136/bmj.f1235
64. Stolz D, Kostikas K, Loeffroth E, et al. Differences in COPD exacerbation risk between women and men: analysis from the UK clinical practice research datalink data. *Chest*. 2019;156(4):674–684. doi:10.1016/j.chest.2019.04.107
65. Svedater H, Leather D, Robinson T, Doll H, Nafees B, Bradshaw L. Evaluation and quantification of treatment preferences for patients with asthma or COPD using discrete choice experiment surveys. *Respir Med*. 2017;132:76–83. doi:10.1016/j.rmed.2017.09.010
66. Thomas M, Radwan A, Stonham C, Marshall S. COPD exacerbation frequency, pharmacotherapy and resource use: an observational study in UK primary care. *COPD*. 2014;11(3):300–309. doi:10.3109/15412555.2013.841671
67. Trethewey SP, Edgar RG, Morlet J, Mukherjee R, Turner AM. Late presentation of acute hypercapnic respiratory failure carries a high mortality risk in COPD patients treated with ward-based NIV. *Respir Med*. 2019;151:128–132. doi:10.1016/j.rmed.2019.04.013
68. Trethewey SP, Edgar RG, Morlet J, Mukherjee R, Turner AM. Temporal trends in survival following ward-based NIV for acute hypercapnic respiratory failure in patients with COPD. *CRJ*. 2019;13(3):184–188. doi:10.1111/crj.12994
69. Turner AM, Lim WS, Rodrigo C, Welham SA, Calvert JM. A care-bundles approach to improving standard of care in AECOPD admissions: results of a national project. *Thorax*. 2015;70(10):992–994. doi:10.1136/thoraxjnl-2015-206833
70. Verduri A, Carter B, Laraman J, et al. Frailty and its influence on mortality and morbidity in COPD: a systematic review and meta-analysis. *Intern Emerg Med*. 2023;18(8):2423–2434. doi:10.1007/s11739-023-03405-6
71. Whittaker H, Rothnie KJ, Quint JK. Exploring the impact of varying definitions of exacerbations of chronic obstructive pulmonary disease in routinely collected electronic medical records. *PLoS One*. 2023;18(11):e0292876. doi:10.1371/journal.pone.0292876
72. Whittaker H, Rubino A, Mullerova H, et al. Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis*. 2022;17:427–437. doi:10.2147/COPD.S346591
73. Williams NP, Coombs NA, Johnson MJ, et al. Seasonality, risk factors and burden of community-acquired pneumonia in COPD patients: a population database study using linked health care records. *Int J Chron Obstruct Pulmon Dis*. 2017;12:313–322. doi:10.2147/COPD.S121389
74. Elkhenini HF, Davis KJ, Stein ND, et al. Using an electronic medical record (EMR) to conduct clinical trials: Salford Lung Study feasibility. *BMC Med Inform Decis Mak*. 2015;15:8. doi:10.1186/s12911-015-0132-z
75. Hyams C, Qian G, Nava G, et al. Impact of SARS-CoV-2 infective exacerbation of chronic obstructive pulmonary disease on clinical outcomes in a prospective cohort study of hospitalised adults. *J R Soc Med*. 2023;116(11):371–385. doi:10.1177/01410768231184162
76. Oshagbemi OA, Keene SJ, Driessen JHM, et al. Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013. *Respir Med*. 2018;144:1–6. doi:10.1016/j.rmed.2018.09.010
77. Adrish M, Nannaka VB, Cano EJ, Bajantri B, Diaz-Fuentes G. Significance of NT-pro-BNP in acute exacerbation of COPD patients without underlying left ventricular dysfunction. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1183–1189. doi:10.2147/COPD.S134953
78. Alqahtani F, Welle GA, Elsisy MF, et al. Incidence, characteristics, and outcomes of acute myocardial infarction among patients admitted with acute exacerbation of chronic obstructive lung disease. *COPD*. 2020;17(3):261–268. doi:10.1080/15412555.2020.1757054
79. Alqahtani JS, Njoku CM, Bereznicki B, et al. Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis. *Eur Respir Rev*. 2020;29(156):190166. doi:10.1183/16000617.0166-2019
80. Andrijevic I, Milutinovic S, Lozanov Crvenkovic Z, et al. N-Terminal Prohormone of Brain Natriuretic Peptide (NT-proBNP) as a diagnostic biomarker of left ventricular systolic dysfunction in patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD). *Lung*. 2018;196(5):583–590. doi:10.1007/s00408-018-0137-3
81. Bahloul M, Chaari A, Tounsi A, et al. Incidence and impact outcome of pulmonary embolism in critically ill patients with severe exacerbation of chronic obstructive pulmonary diseases. *CRJ*. 2015;9(3):270–277. doi:10.1111/crj.12131
82. Blasi F, Neri L, Centanni S, Falcone F, Di Maria G. Clinical characterization and treatment patterns for the frequent exacerbator phenotype in chronic obstructive pulmonary disease with severe or very severe airflow limitation. *COPD*. 2017;14(1):15–22. doi:10.1080/15412555.2016.1232380

83. Boixeda R, Almagro P, Diez-Manglano J, et al. Bacterial flora in the sputum and comorbidity in patients with acute exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10:2581–2591. doi:10.2147/COPD.S88702
84. Buhr RG, Jackson NJ, Dubinett SM, Kominski GF, Mangione CM, Ong MK. Factors associated with differential readmission diagnoses following acute exacerbations of chronic obstructive pulmonary disease. *J Hosp Med*. 2020;15(4):219–227. doi:10.12788/jhm.3367
85. Campo G, Pavasini R, Malagu M, et al. Relationship between troponin elevation, cardiovascular history and adverse events in patients with acute exacerbation of COPD. *COPD*. 2015;12(5):560–567. doi:10.3109/15412555.2014.995293
86. Cao Y, Xing Z, Long H, et al. Predictors of mortality in COPD exacerbation cases presenting to the respiratory intensive care unit. *Respir Res*. 2021;22(1):77. doi:10.1186/s12931-021-01657-4
87. Castillo A, Edriss H, Selvan K, Nugent K. Characteristics of patients with congestive heart failure or chronic obstructive pulmonary disease readmissions within 30 days following an acute exacerbation. *Qual Manag Health Care*. 2017;26(3):152–159. doi:10.1097/QMH.0000000000000143
88. Cerezo Lajas A, Gutierrez Gonzalez E, Llorente Parrado C, Puente Maestu L, de Miguel-Diez J. Readmission due to exacerbation of COPD: associated factors. *Lung*. 2018;196(2):185–193. doi:10.1007/s00408-018-0093-y
89. Cui Y, Zhan Z, Ma Y, et al. Clinical and economic burden of comorbid coronary artery disease in patients with acute exacerbation of chronic obstructive pulmonary disease: sex differences in a nationwide cohort study. *Respir Res*. 2022;23(1):28. doi:10.1186/s12931-022-01945-7
90. D'Urzo A, Rennard S, Kerwin E, et al. A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of Aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease. *Respir Med*. 2017;125:39–48. doi:10.1016/j.rmed.2017.02.008
91. Dentali F, Pomeroy F, Micco PD, et al. Prevalence and risk factors for pulmonary embolism in patients with suspected acute exacerbation of COPD: a multi-center study. *Eur J Int Med*. 2020;80:54–59. doi:10.1016/j.ejim.2020.05.006
92. Di Raimondo D, Pirera E, Pintus C, et al. The Role of the Cumulative Illness Rating Scale (CIRS) in estimating the impact of Comorbidities on Chronic Obstructive Pulmonary Disease (COPD) outcomes: a pilot study of the MACH (Multidimensional Approach for COPD and High Complexity) Study. *J Pers Med*. 2023;13(12). doi:10.3390/jpm13121674
93. Domenech A, Munoz-Montiel A, Garcia-Casares N, et al. High risk of subclinical atherosclerosis in COPD exacerbator phenotype. *Respir Med*. 2018;141:165–171. doi:10.1016/j.rmed.2018.07.004
94. Einvik G, Bhatnagar R, Holmedahl NH, Neukamm A, Omland T, Soyseth V. Premature ventricular complex is more prevalent during acute exacerbated than stable states of chronic obstructive pulmonary disease, and is related to cardiac troponin T. *COPD*. 2017;14(3):318–323. doi:10.1080/15412555.2017.1298085
95. Elvekjaer M, Aasvang EK, Olsen RM, et al. Physiological abnormalities in patients admitted with acute exacerbation of COPD: an observational study with continuous monitoring. *J Clin Monit Comput*. 2020;34(5):1051–1060. doi:10.1007/s10877-019-00415-8
96. Epstein D, Nasser R, Mashiah T, Azzam ZS, Berger G. Increased red cell distribution width: a novel predictor of adverse outcome in patients hospitalized due to acute exacerbation of chronic obstructive pulmonary disease. *Respir Med*. 2018;136:1–7. doi:10.1016/j.rmed.2018.01.011
97. Escande W, Duva Pentiah A, Coisne A, et al. Left ventricular myocardial performance index predicts poor outcome during COPD exacerbation. *Int J Cardiol*. 2014;173(3):575–579. doi:10.1016/j.ijcard.2014.03.115
98. Esteban C, Castro-Acosta A, Alvarez-Martinez CJ, Capelastegui A, Lopez-Campos JL, Pozo-Rodriguez F. Predictors of one-year mortality after hospitalization for an exacerbation of COPD. *BMC Pulm Med*. 2018;18(1):18. doi:10.1186/s12890-018-0574-z
99. Freeman CM, Martinez CH, Todt JC, et al. Acute exacerbations of chronic obstructive pulmonary disease are associated with decreased CD4+ & CD8+ T cells and increased growth & differentiation factor-15 (GDF-15) in peripheral blood. *Respir Res*. 2015;16(1):94. doi:10.1186/s12931-015-0251-1
100. Genao L, Durham MT, Mi X, Todd JL, Whitson HE, Curtis LH. Early and long-term outcomes of older adults after acute care encounters for chronic obstructive pulmonary disease exacerbation. *Ann Am Thorac Soc*. 2015;12(12):1805–1812. doi:10.1513/AnnalsATS.201504-250OC
101. Germini F, Veronese G, Marcucci M, et al. COPD exacerbations in the emergency department: epidemiology and related costs. A retrospective cohort multicentre study from the Italian Society of Emergency Medicine (SIMEU). *Eur J Int Med*. 2018;51:74–79. doi:10.1016/j.ejim.2018.01.010
102. Goto T, Shimada YJ, Faridi MK, Camargo CA, Hasegawa K. Incidence of acute cardiovascular event after acute exacerbation of COPD. *J Gen Intern Med*. 2018;33(9):1461–1468. doi:10.1007/s11606-018-4518-3
103. Grymonprez M, Vakaet V, Kavousi M, et al. Chronic obstructive pulmonary disease and the development of atrial fibrillation. *Int J Cardiol*. 2019;276:118–124. doi:10.1016/j.ijcard.2018.09.056
104. Guo X, Nie H, Chen Q, et al. The role of plasma N-terminal brain natriuretic pro-peptide in diagnosing elderly patients with acute exacerbation of COPD concurrent with left heart failure. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2931–2940. doi:10.2147/COPD.S164671
105. Gyalai-Korpos I, Ancusa O, Dragomir T, Tomescu MC, Marincu I. Factors associated with prolonged hospitalization, readmission, and death in elderly heart failure patients in western Romania. *Clin Interv Aging*. 2015;10:561–568. doi:10.2147/CIA.S79569
106. Han MK, Quibrera PM, Carretta EE, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med*. 2017;5(8):619–626. doi:10.1016/S2213-2600(17)30207-2
107. Hirayama A, Goto T, Shimada YJ, Faridi MK, Camargo CA, Hasegawa K. Acute exacerbation of chronic obstructive pulmonary disease and subsequent risk of emergency department visits and hospitalizations for atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2018;11(9):e006322. doi:10.1161/CIRCEP.118.006322
108. Hoffmann C, Hanisch M, Heinsohn JB, et al. Increased vulnerability of COPD patient groups to urban climate in view of global warming. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3493–3501. doi:10.2147/COPD.S174148
109. Hoiseith AD, Brynildsen J, Hagve TA, et al. The influence of heart failure co-morbidity on high-sensitivity troponin T levels in COPD exacerbation in a prospective cohort study: data from the Akershus cardiac examination (ACE) 2 study. *Biomarkers*. 2016;21(2):173–179. doi:10.3109/1354750X.2015.1126645
110. Hoiseith AD, Omland T, Karlsson BD, Brekke PH, Soyseth V. Standardized evaluation of lung congestion during COPD exacerbation better identifies patients at risk of dying. *Int J Chron Obstruct Pulmon Dis*. 2013;8:621–629. doi:10.2147/COPD.S52854
111. Hu G, Wu Y, Zhou Y, Yu Y, Liang W, Ran P. Cystatin C as a predictor of in-hospital mortality after exacerbation of COPD. *Respir Care*. 2016;61(7):950–957. doi:10.4187/respcare.04034

112. Hu WP, Lhamo T, Liu D, et al. Development of a nomogram to predict the risk of 30-day re-exacerbation for patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease. *COPD*. 2019;16(2):160–167. doi:10.1080/15412555.2019.1606187
113. Hu WP, Lhamo T, Zhang FY, et al. Predictors of acute cardiovascular events following acute exacerbation period for patients with COPD: a nested case-control study. *BMC Cardiovasc Disord*. 2020;20(1):518. doi:10.1186/s12872-020-01803-8
114. Jimenez D, Agusti A, Tabernero E, et al. Effect of a pulmonary embolism diagnostic strategy on clinical outcomes in patients hospitalized for COPD exacerbation: a randomized clinical trial. *JAMA*. 2021;326(13):1277–1285. doi:10.1001/jama.2021.14846
115. Johannesdottir SA, Christiansen CF, Johansen MB, et al. Hospitalization with acute exacerbation of chronic obstructive pulmonary disease and associated health resource utilization: a population-based Danish cohort study. *J Med Econ*. 2013;16(7):897–906. doi:10.3111/13696998.2013.800525
116. Johannessen O, Uthaug Reite F, Bhatnagar R, Ovrebotten T, Einvik G, Myhre PL. Lung ultrasound to assess pulmonary congestion in patients with acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis*. 2023;18:693–703. doi:10.2147/COPD.S396855
117. Kanhere N, Couch MJ, Kowalik K, et al. Correlation of lung clearance index with hyperpolarized (129)Xe magnetic resonance imaging in pediatric subjects with cystic fibrosis. *Am J Respir Crit Care Med*. 2017;196(8):1073–1075. doi:10.1164/rccm.201611-2228LE
118. Kaya H, Zorlu A, Yucel H, et al. Cancer antigen-125 levels predict long-term mortality in chronic obstructive pulmonary disease. *Biomarkers*. 2015;20(2):162–167. doi:10.3109/1354750X.2015.1045033
119. Kemdem A, Lemaître F, Lovat R, Siraux V, Dillien P, Dive F. Acute hypoxic pulmonary hypertension associated with right heart failure. *Acta Cardiol*. 2020;75(6):544–548. doi:10.1080/00015385.2019.1634333
120. Kim Y, Kim YJ, Kang YM, Cho WK. Exploring the impact of number and type of comorbidities on the risk of severe COPD exacerbations in Korean Population: a Nationwide Cohort Study. *BMC Pulm Med*. 2021;21(1):151. doi:10.1186/s12890-021-01497-4
121. Kouraichi C, Sekma A, Bel Haj Ali K, et al. Value of inferior vena cava collapsibility index as marker of heart failure in chronic obstructive pulmonary disease exacerbation. *BMC Cardiovasc Disord*. 2023;23(1):579. doi:10.1186/s12872-023-03585-1
122. Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. *Am J Respir Crit Care Med*. 2018;198(1):51–57. doi:10.1164/rccm.201711-2239OC
123. Labonte L, Coulombe P, Zago M, Bourbeau J, Baglolle CJ. Alterations in the expression of the NF-kappaB family member RelB as a novel marker of cardiovascular outcomes during acute exacerbations of chronic obstructive pulmonary disease. *PLoS One*. 2014;9(11):e112965. doi:10.1371/journal.pone.0112965
124. Lahousse L, Niemeijer MN, van den Berg ME, et al. Chronic obstructive pulmonary disease and sudden cardiac death: the Rotterdam study. *Eur Heart J*. 2015;36(27):1754–1761. doi:10.1093/eurheartj/ehv121
125. Lai Y, DeNardo A, Niranjana S, Sriram KB. Increased QT dispersion is associated with reduced overall survival in patients with acute exacerbations of chronic obstructive pulmonary disease. *Hosp Pract*. 2017;45(5):253–257. doi:10.1080/21548331.2017.1375373
126. Lasman N, Shalom M, Turpashvili N, et al. Baseline low ALT activity is associated with increased long-term mortality after COPD exacerbations. *BMC Pulm Med*. 2020;20(1):133. doi:10.1186/s12890-020-1169-z
127. Lau CS, Siracuse BL, Chamberlain RS. Readmission after COPD exacerbation scale: determining 30-day readmission risk for COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1891–1902. doi:10.2147/COPD.S136768
128. Lauridsen MD, Valentin JB, Strange JE, et al. Mortality in patients with chronic obstructive pulmonary disorder undergoing transcatheter aortic valve replacement: the importance of chronic obstructive pulmonary disease exacerbation. *Am Heart J*. 2023;262:100–109. doi:10.1016/j.ahj.2023.04.016
129. Lin CS, Shih CC, Yeh CC, et al. Risk of stroke and post-stroke adverse events in patients with exacerbations of chronic obstructive pulmonary disease. *PLoS One*. 2017;12(1):e0169429. doi:10.1371/journal.pone.0169429
130. Lin WC, Chen CW, Lu CL, et al. The association between recent hospitalized COPD exacerbations and adverse outcomes after percutaneous coronary intervention: a nationwide cohort study. *Int J Chron Obstruct Pulmon Dis*. 2019;14:169–179. doi:10.2147/COPD.S187345
131. Liu Y, Liu X, Lin G, Sun L, Li H, Xie C. Decreased CD34+ cell number is correlated with cardiac dysfunction in patients with acute exacerbation of COPD. *Heart Lung Circ*. 2014;23(9):875–882. doi:10.1016/j.hlc.2014.03.008
132. Mahboub B, Alzaabi A, Iqbal MN, et al. Comorbidities associated with COPD in the Middle East and North Africa region: association with severity and exacerbations. *Int J Chron Obstruct Pulmon Dis*. 2016;11:273–280. doi:10.2147/COPD.S90626
133. Malerba M, Olivini A, Radaeli A, Ricciardolo FL, Cline E. Platelet activation and cardiovascular comorbidities in patients with chronic obstructive pulmonary disease. *Curr Med Res Opin*. 2016;32(5):885–891. doi:10.1185/03007995.2016.1149054
134. Marcun R, Stankovic I, Vidakovic R, et al. Prognostic implications of heart failure with preserved ejection fraction in patients with an exacerbation of chronic obstructive pulmonary disease. *Intern Emerg Med*. 2016;11(4):519–527. doi:10.1007/s11739-015-1319-0
135. Matamis D, Tsagourias M, Papathanasiou A, et al. Targeting occult heart failure in intensive care unit patients with acute chronic obstructive pulmonary disease exacerbation: effect on outcome and quality of life. *J Crit Care*. 2014;29(2):315.e317–314. doi:10.1016/j.jccr.2013.11.011
136. McGarvey L, Lee AJ, Roberts J, Gruffydd-Jones K, McKnight E, Haughey J. Characterisation of the frequent exacerbator phenotype in COPD patients in a large UK primary care population. *Respir Med*. 2015;109(2):228–237. doi:10.1016/j.rmed.2014.12.006
137. Mir T, Uddin M, Khalil A, et al. Mortality outcomes associated with invasive aspergillosis among acute exacerbation of chronic obstructive pulmonary disease patient population. *Respir Med*. 2022;191:106720. doi:10.1016/j.rmed.2021.106720
138. Monsour E, Rodriguez LM, Abdelmasih R, Tuna K, Abusaada K. Characteristics and outcomes of diabetic patients with acute exacerbation of COPD. *J Diabetes Metab Disord*. 2021;20(1):461–466. doi:10.1007/s40200-021-00766-7
139. Mullerova H, Marshall J, de Nigris E, et al. Association of COPD exacerbations and acute cardiovascular events: a systematic review and meta-analysis. *Ther Adv Respir Dis*. 2022;16:17534666221113647. doi:10.1177/17534666221113647
140. Mullerova H, Shukla A, Hawkins A, Quint J. Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. *BMJ Open*. 2014;4(12):e006171. doi:10.1136/bmjopen-2014-006171
141. Munoz-Esquerre M, Ferreira JL, Huertas D, et al. Impact of acute exacerbations on platelet reactivity in chronic obstructive pulmonary disease patients. *Int J Chron Obstruct Pulmon Dis*. 2018;13:141–148. doi:10.2147/COPD.S152660
142. Neef PA, McDonald CF, Burrell LM, Irving LB, Johnson DF, Steinfert DP. Beta-blockers are under-prescribed in patients with chronic obstructive pulmonary disease and co-morbid cardiac disease. *Intern Med J*. 2016;46(11):1336–1340. doi:10.1111/imj.13240

143. Nguyen PL, Uddin MM, Mir T, et al. Trends in incidence, and mortality of acute exacerbation of chronic obstructive pulmonary disease in the United States Emergency Department (2010–2018). *COPD*. 2021;18(5):567–575. doi:10.1080/15412555.2021.1979500
144. Nishimura K, Nishimura T, Onishi K, Oga T, Hasegawa Y, Jones PW. Changes in plasma levels of B-type natriuretic peptide with acute exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2014;9:155–162. doi:10.2147/COPD.S55143
145. Ottiger M, Nickler M, Steuer C, et al. Gut, microbiota-dependent trimethylamine-N-oxide is associated with long-term all-cause mortality in patients with exacerbated chronic obstructive pulmonary disease. *Nutrition*. 2018;45:135–141.e131. doi:10.1016/j.nut.2017.07.001
146. Ovchinnikova ES, Schmitter D, Vegter EL, et al. Signature of circulating microRNAs in patients with acute heart failure. *Eur J Heart Fail*. 2016;18(4):414–423. doi:10.1002/ehf.332
147. Patel AR, Kowlessar BS, Donaldson GC, et al. Cardiovascular risk, myocardial injury, and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;188(9):1091–1099. doi:10.1164/rccm.201306-1170OC
148. Piquet J, Chavaillon JM, David P, et al. High-risk patients following hospitalisation for an acute exacerbation of COPD. *Eur Respir J*. 2013;42(4):946–955. doi:10.1183/09031936.00180312
149. Pizarro C, Herweg-Steffens N, Buchenroth M, et al. Invasive coronary angiography in patients with acute exacerbated COPD and elevated plasma troponin. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2081–2089. doi:10.2147/COPD.S110746
150. Portegies ML, Lahousse L, Joos GF, et al. Chronic Obstructive Pulmonary Disease and the Risk of Stroke. The Rotterdam Study. *Am J Respir Crit Care Med*. 2016;193(3):251–258. doi:10.1164/rccm.201505-0962OC
151. Rea F, Calusi G, Franchi M, et al. Adherence of elderly patients with cardiovascular disease to statins and the risk of exacerbation of chronic obstructive pulmonary disease: evidence from an Italian real-world investigation. *Drugs Aging*. 2018;35(12):1099–1108. doi:10.1007/s40266-018-0600-0
152. Reiger G, Zwick R, Lamprecht B, Kahler C, Burghuber OC, Valipour A. Phenotypes of COPD in an Austrian population: national data from the POPE study. *Wien Klin Wochenschr*. 2018;130(11–12):382–389. doi:10.1007/s00508-018-1347-7
153. Reilev M, Pottegard A, Lykkegaard J, Sondergaard J, Ingebrigtsen TS, Hallas J. Increased risk of major adverse cardiac events following the onset of acute exacerbations of COPD. *Respirology*. 2019;24(12):1183–1190. doi:10.1111/resp.13620
154. Rockenschaub P, Jhass A, Freemantle N, et al. Opportunities to reduce antibiotic prescribing for patients with COPD in primary care: a cohort study using electronic health records from the Clinical Practice Research Datalink (CPRD). *J Antimicrob Chemother*. 2020;75(1):243–251. doi:10.1093/jac/dkz411
155. Rothnie KJ, Connell O, Mullerova H, et al. Myocardial infarction and ischemic stroke after exacerbations of chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2018;15(8):935–946. doi:10.1513/AnnalsATS.201710-815OC
156. Rusinowicz T, Zielonka TM, Zycinska K. Cardiac arrhythmias in patients with exacerbation of COPD. *Adv Exp Med Biol*. 2017;1022:53–62. doi:10.1007/5584_2017_41
157. Saleh A, Lopez-Campos JL, Hartl S, Pozo-Rodriguez F, Roberts CM; European COPD Audit team. The effect of incidental consolidation on management and outcomes in COPD exacerbations: data from the European COPD audit. *PLoS One*. 2015;10(7):e0134004. doi:10.1371/journal.pone.0134004
158. Santibanez M, Garrastazu R, Ruiz-Nunez M, et al. Predictors of hospitalized exacerbations and mortality in chronic obstructive pulmonary disease. *PLoS One*. 2016;11(6):e0158727. doi:10.1371/journal.pone.0158727
159. Santoro F, Ieva R, Ferraretti A, et al. Diffuse ST-elevation following J-wave presentation as an uncommon electrocardiogram pattern of Tako-Tsubo cardiomyopathy. *Heart Lung*. 2013;42(5):375–378. doi:10.1016/j.hrtlng.2013.05.002
160. Santus P, Franceschi E, Pini S, et al. Switching to nebulised short acting bronchodilators does not increase the risk of arrhythmia in patients hospitalized with a COPD exacerbation. *Pharmacol Res*. 2021;173:105915. doi:10.1016/j.phrs.2021.105915
161. Shafuddin E, Chang CL, Cooray M, et al. Cardiac dysfunction in exacerbations of chronic obstructive pulmonary disease is often not detected by electrocardiogram and chest radiographs. *Intern Med J*. 2019;49(6):761–769. doi:10.1111/imj.14144
162. Simons SO, Elliott A, Sastry M, et al. Chronic obstructive pulmonary disease and atrial fibrillation: an interdisciplinary perspective. *Eur Heart J*. 2021;42(5):532–540. doi:10.1093/eurheartj/ehaa822
163. Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2013;10(2):81–89. doi:10.1513/AnnalsATS.201208-043OC
164. Slenter RH, Sprooten RT, Kotz D, Wesseling G, Wouters EF, Rohde GG. Predictors of 1-year mortality at hospital admission for acute exacerbations of chronic obstructive pulmonary disease. *Respiration*. 2013;85(1):15–26. doi:10.1159/000342036
165. Soltani A, Reid D, Wills K, Walters EH. Prospective outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease presenting to hospital: a generalisable clinical audit. *Intern Med J*. 2015;45(9):925–933. doi:10.1111/imj.12816
166. Spece LJ, Epler EM, Donovan LM, et al. Role of comorbidities in treatment and outcomes after chronic obstructive pulmonary disease exacerbations. *Ann Am Thorac Soc*. 2018;15(9):1033–1038. doi:10.1513/AnnalsATS.201804-255OC
167. Stiell IG, Perry JJ, Clement CM, et al. Clinical validation of a risk scale for serious outcomes among patients with chronic obstructive pulmonary disease managed in the emergency department. *CMAJ*. 2018;190(48):E1406–E1413. doi:10.1503/cmaj.180232
168. Stoll P, Foerster S, Virchow JC, Lommatzsch M. Overweight is a predictor of long-term survival in hospitalised patients with exacerbations of COPD. *Respir Med*. 2016;116:59–62. doi:10.1016/j.rmed.2016.05.016
169. Su X, Lei T, Yu H, et al. NT-proBNP in different patient groups of COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2023;18:811–825. doi:10.2147/COPD.S396663
170. Tashiro H, Kurihara Y, Takahashi K, et al. Clinical features of Japanese patients with exacerbations of chronic obstructive pulmonary disease. *BMC Pulm Med*. 2020;20(1):318. doi:10.1186/s12890-020-01362-w
171. Terzano C, Romani S, Conti V, Paone G, Oriolo F, Vitarelli A. Atrial fibrillation in the acute, hypercapnic exacerbations of COPD. *Eur Rev Med Pharmacol Sci*. 2014;18(19):2908–2917.
172. Terzano C, Romani S, Gaudio C, Pelliccia F, Srao M, Vitarelli A. Right heart functional changes in the acute, hypercapnic exacerbations of COPD. *BioMed Res Int*. 2014;2014:596051. doi:10.1155/2014/596051
173. Vallabhajosyula S, Haddad TM, Sundaragiri PR, et al. Role of B-type natriuretic peptide in predicting in-hospital outcomes in acute exacerbation of chronic obstructive pulmonary disease with preserved left ventricular function: a 5-year retrospective analysis. *J Intensive Care Med*. 2018;33(11):635–644. doi:10.1177/0885066616682232

174. Van Oekelen O, Vermeersch K, Everaerts S, Vandenberk B, Willems R, Janssens W. Significance of prolonged QTc in acute exacerbations of COPD requiring hospitalization. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1937–1947. doi:10.2147/COPD.S157630
175. Wade RC, Simmons JP, Boueiz A, et al. Pulmonary artery enlargement is associated with exacerbations and mortality in ever-smokers with preserved ratio impaired spirometry. *Am J Respir Crit Care Med*. 2021;204(4):481–485. doi:10.1164/rccm.202103-0619LE
176. Wang X, Jiang Z, Chen B, et al. Cardiac autonomic function in patients with acute exacerbation of chronic obstructive pulmonary disease with and without ventricular tachycardia. *BMC Pulm Med*. 2016;16(1):124. doi:10.1186/s12890-016-0287-0
177. Wang Y, Zheng Y, Zhai YL, Liu FQ, Ding N. Comparative analysis of MCP-1 and TF in elderly patients with acute exacerbations of COPD and its clinical significance. *Eur Rev Med Pharmacol Sci*. 2015;19(2):215–219.
178. Wang WQ, Huang HL, Zhu S, Nie X, Li GX. High-sensitivity cardiac troponin T in patients with acute myocardial infarction in acute exacerbation of chronic obstructive pulmonary disease. *Clin Lab*. 2015;61(8):1083–1093. doi:10.7754/clin.lab.2015.150105
179. Wang M, Lin EP, Huang LC, Li CY, Shyr Y, Lai CH. Mortality of cardiovascular events in patients with COPD and preceding hospitalization for acute exacerbation. *Chest*. 2020;158(3):973–985. doi:10.1016/j.chest.2020.02.046
180. Wedzicha JA, Dahl R, Buhl R, et al. Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients. *Respir Med*. 2014;108(10):1498–1507. doi:10.1016/j.rmed.2014.07.011
181. Wells JM, Morrison JB, Bhatt SP, Nath H, Dransfield MT. Pulmonary artery enlargement is associated with cardiac injury during severe exacerbations of COPD. *Chest*. 2016;149(5):1197–1204. doi:10.1378/chest.15-1504
182. Westerik JA, Metting EI, van Boven JF, Tiersma W, Kocks JW, Schermer TR. Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. *Respir Res*. 2017;18(1):31. doi:10.1186/s12931-017-0512-2
183. Windsor C, Herrett E, Smeeth L, Quint JK. No association between exacerbation frequency and stroke in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:217–225. doi:10.2147/COPD.S95775
184. Yen FS, Chen W, Wei JC, Hsu CC, Hwu CM. Effects of metformin use on total mortality in patients with type 2 diabetes and chronic obstructive pulmonary disease: a matched-subject design. *PLoS One*. 2018;13(10):e0204859. doi:10.1371/journal.pone.0204859
185. Wu HX, Zhuo KQ, Cheng DY. Peripheral blood eosinophil as a biomarker in outcomes of acute exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2019;14:3003–3015. doi:10.2147/COPD.S226783
186. Xiao X, Han H, Wu C, et al. Prevalence of atrial fibrillation in hospital encounters with end-stage COPD on home oxygen: national trends in the United States. *Chest*. 2019;155(5):918–927. doi:10.1016/j.chest.2018.12.021
187. Zhao X, Su R, Hu R, et al. Sarcopenia index as a predictor of clinical outcomes among older adult patients with acute exacerbation of chronic obstructive pulmonary disease: a cross-sectional study. *Clin Lab*. 2023;23(1):89. doi:10.1186/s12877-023-03784-7
188. Yao C, Wang L, Shi F, et al. Optimized combination of circulating biomarkers as predictors of prognosis in AECOPD patients complicated with heart failure. *Int J Med Sci*. 2021;18(7):1592–1599. doi:10.7150/ijms.52405
189. Zhu M, Dai L, Wan L, Zhang S, Peng H. Dynamic increase of red cell distribution width predicts increased risk of 30-day readmission in patients with acute exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2021;16:393–400. doi:10.2147/COPD.S291833
190. Zuur-Telgen M, VanderValk P, van der Palen J, Kerstjens HA, Brusse-Keizer M. Stable state proadrenomedullin level in COPD patients: a validation study. *COPD*. 2017;14(2):219–227. doi:10.1080/15412555.2016.1250254
191. Aldabayan YS, Ridsdale HA, Alrajeh AM, et al. Pulmonary rehabilitation, physical activity and aortic stiffness in COPD. *Respir Res*. 2019;20(1):166. doi:10.1186/s12931-019-1135-6
192. Anderson WJ, Lipworth BJ, Rekhraj S, Struthers AD, George J. Left ventricular hypertrophy in COPD without hypoxemia: the elephant in the room? *Chest*. 2013;143(1):91–97. doi:10.1378/chest.12-0775
193. Bloom CI, Ricciardi F, Smeeth L, Stone P, Quint JK. Predicting COPD 1-year mortality using prognostic predictors routinely measured in primary care. *BMC Med*. 2019;17(1):73. doi:10.1186/s12916-019-1310-0
194. Cuthbert JJ, Kearsley JW, Kazmi S, et al. The impact of heart failure and chronic obstructive pulmonary disease on mortality in patients presenting with breathlessness. *Clin Res Cardiol*. 2019;108(2):185–193. doi:10.1007/s00392-018-1342-z
195. Hanlon P, Nicholl BI, Jani BD, et al. Examining patterns of multimorbidity, polypharmacy and risk of adverse drug reactions in chronic obstructive pulmonary disease: a cross-sectional UK Biobank study. *BMJ Open*. 2018;8(1):e018404. doi:10.1136/bmjopen-2017-018404
196. John ME, Cockcroft JR, McKeever TM, et al. Cardiovascular and inflammatory effects of simvastatin therapy in patients with COPD: a randomized controlled trial. *Int J Chron Obstruct Pulmon Dis*. 2015;10:211–221. doi:10.2147/COPD.S76061
197. John M, McKeever TM, Haddad MA, et al. Traditional and emerging indicators of cardiovascular risk in chronic obstructive pulmonary disease. *Chron Respir Dis*. 2016;13(3):247–255. doi:10.1177/1479972316636995
198. Lawson CA, Mamas MA, Jones PW, et al. Association of medication intensity and stages of airflow limitation with the risk of hospitalization or death in patients with heart failure and chronic obstructive pulmonary disease. *JAMA Network Open*. 2018;1(8):e185489. doi:10.1001/jamanetworkopen.2018.5489
199. Uddin MJ, Groenwold RH, de Boer A, et al. Evaluating different physician's prescribing preference based instrumental variables in two primary care databases: a study of inhaled long-acting beta2-agonist use and the risk of myocardial infarction. *Pharmacoepidemiol Drug Saf*. 2016;25 Suppl 1:132–141. doi:10.1002/pds.3860
200. Smith MC, Ashdown HF, Sheppard JP, Butler CC, Bankhead C. Statin prescription in patients with chronic obstructive pulmonary disease and risk of exacerbations: a retrospective cohort study in the Clinical Practice Research Datalink. *BMJ Open*. 2021;11(12):e050757. doi:10.1136/bmjopen-2021-050757
201. Smith D, Du Rand I, Addy CL, et al. British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease. *Thorax*. 2020;75(5):370–404. doi:10.1136/thoraxjnl-2019-213929
202. Hippisley-Cox J, Coupland CAC, Bafadhel M, et al. Development and validation of a new algorithm for improved cardiovascular risk prediction. *Nat Med*. 2024;30(5):1440–1447. doi:10.1038/s41591-024-02905-y
203. Jones P, Alzaabi A, Casas Herrera A, et al. Understanding the gaps in the reporting of COPD exacerbations by patients: a review. *COPD*. 2024;21(1):2316594. doi:10.1080/15412555.2024.2316594
204. Karch A, Vogelmeier C, Welte T, et al. The German COPD cohort COSYCONET: aims, methods and descriptive analysis of the study population at baseline. *Respir Med*. 2016;114:27–37. doi:10.1016/j.rmed.2016.03.008

205. Hutchinson A, Barclay-Kingle N, Galvin K, Johnson MJ. Living with breathlessness: a systematic literature review and qualitative synthesis. *Eur Respir J*. 2018;51(2):1701477. doi:10.1183/13993003.01477-2017
206. Hopkinson NS, Baxter N. Breathing SPACE-a practical approach to the breathless patient. *NPJ Prim Care Respir Med*. 2017;27(1):5. doi:10.1038/s41533-016-0006-6
207. NHS England. Respiratory Disease: Better care for major health conditions. NHS Long Term Plan; 2019. Available from: <https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-care-quality-and-outcomes/better-care-for-major-health-conditions/respiratory-disease/>. Accessed November 29, 2024.
208. NHS Confederation. Unlocking reform and financial sustainability: the role of payment mechanisms in improving outcomes and efficiency. NHS Confederation; 2023. Available from: <https://www.nhsconfed.org/publications/unlocking-reform-and-financial-sustainability>. Accessed November 29, 2024.

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