Original Research

Validation of Acute Exacerbation of Chronic Obstructive Pulmonary Disease Recording in Electronic Health Records: A Systematic Review

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Abstract

Objective: Acute exacerbations of COPD (AECOPD) can have severe impacts on patients with the disease and a heavy burden on healthcare resources. Electronic health records (EHRs) are a valuable resource for identifying cases of AECOPD and research. Studies have attempted to validate case definitions of AECOPD and this review aimed to summarise validated AECOPD definitions in EHRs, and to provide guidance on the best algorithms to use to ensure accurate cohorts of AECOPD cases are available for researchers using EHRs.

Methods: MEDLINE and Embase were searched and studies that met the inclusion criteria were reviewed by ≥2 reviewers. Data extracted included the algorithms used to identify AECOPD, the reference standards used to compare against the algorithm, and measures of validity. The risk of bias was assessed using QUADAS-2 adapted for this review.

Results: Out of 2,784 studies found by the search strategy, 12 met the inclusion criteria. The clinical terminology used to build algorithms to detect AECOPD included codes from the International Statistical Classification of Diseases and Related Health Problems (ICD) 9th and 10th editions (ICD-9 and ICD-10), along with Read codes from UK general practices. AECOPD can be identified within EHRs using validated definitions, however the validity of AECOPD definitions vary considerably depending on the algorithm used and the settings they are applied in.

Conclusion: Although there are validated definitions that can be used to identify AECOPD, there is no clear consensus on which provides the highest validity or the most sensitive and specific definition to use.

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Abbreviations: Chronic Obstructive Pulmonary Disease (COPD), Acute Exacerbations of COPD (AECOPD), Electronic Health Records (EHR), International Statistical Classification of Diseases and Related Health Problems (ICD), International Statistical Classification of Diseases and Related Health Problems 9th Edition (ICD-9), International Statistical Classification of Diseases and Related Health Problems 10th Edition (ICD-10), Hospital Episode Statistics (HES), Positive Predictive Value (PPV), Negative Predictive Value (NPV),

Keywords: COPD, exacerbation, electronic health records, validation

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a disease that is characterised by persistent respiratory symptoms including breathlessness, sputum or cough, and airflow limitation due to damage to the airway and/or alveoli (1, 2). COPD is most commonly caused by cigarette smoke, but pollution and occupational exposures are also risk factors for COPD (1, 2) . Patients with COPD can experience episodes of sustained worsening in their symptoms, referred to as an acute exacerbation of COPD (AECOPD), and can be severe enough to require hospitalisation (3). Frequent exacerbations are associated with increased mortality (4) and a decrease in lung function (5), exercise capacity (6) and quality of life (7), and each additional AECOPD increases the risk of a subsequent AECOPD and death (8). Additionally, hospitalisations for AECOPD are very costly and can increase the economic burden on the healthcare services (9-13). In England, the average cost per admission for an AECOPD is estimated to be £1,868 (14), and in the United States for the most severe admissions reportedly as high as an average of $44,909 (11).

Due to the impact of AECOPD admissions on both patients and healthcare services, there is an impetus (15) to complete research on AECOPDs to discover potential interventions to

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reduce their frequency. Electronic health records (EHRs) provide a relatively quick and inexpensive (16) source of data to be able to carry out such studies and are increasingly being utilised in research (17). Diagnoses are recorded in EHRs using a coded clinical terminology set such as International Statistical Classification of Diseases and Related Health Problems (ICD) codes (18), which are widely used in hospital admission discharge summaries and healthcare billing databases globally, consisting of 7 characters of letters and numbers to classify diagnoses. In the United Kingdom, in primary care, diagnoses are commonly recorded in databases as Read codes (now increasingly obsolete) or as SNOMED CT codes which are coded clinical terms used in general practice primary care databases in the National Health Service (NHS) (19).

However, EHRs are not designed with research in mind – their primary focus being to aid physicians in the management of a patient's healthcare (20), or for the purpose of insurance claims (21). For example, the assignment of primary and secondary ICD discharge diagnosis codes for hospitalized patients is often done for reimbursement and therefore may be influenced by the anticipated reimbursement for a diagnosis, bringing into question the validity of these data for the identification of patients with a specific condition (22). Furthermore, different databases (and even different clinicians entering records into those databases) use different coding strategies to classify AECOPD and there is a lack of consensus over which strategies and definitions to use. To ensure studies utilising EHRs are examining the condition of interest and are not at risk of misclassification, it is important to use validated definitions of the condition of interest (23, 24). A validated definition will commonly take the form of a list of codes of a particular clinical terminology, along with an algorithm of how to apply those codes. A validation study will then give estimates on the likelihood of a case detected with the algorithm being a true case (25). Measures of validation

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include positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity.

A previous systematic scoping review by Sivakumaran et al., (26) aimed to identify how individuals with COPD are identified within EHRs and found widespread variation in the definitions used to identify people with COPD. Of the 185 eligible studies, only 7 used a case definition which had been validated against a reference standard in the same dataset. They argued that the inconsistencies in methods for identifying people with COPD in electronic health records is minimising the potential for harnessing EHRs worldwide. To our knowledge there has not been another systematic review examining the identification and validation of *acute exacerbations* of COPD in EHRs.

Therefore, in this systematic review we aimed to summarise all validated definitions of AECOPD for use in EHRs and administrative claims databases, and in cases where multiple similar definitions are available, provide guidance on the best algorithm to use to ensure an accurate cohort of AECOPD cases is available for researchers using EHRs.

Methods

MEDLINE and Embase (via the Ovid interface) were searched using keywords and Medical Subject Headings (MeSH) terms (27, 28) related to 'exacerbation of COPD', 'electronic health records' or 'administrative claims database', and 'validation', including any relevant synonyms. The full search strategy can be found in **Supplementary File 1**. Methodology developed by Benchimol et al. (29), along with search strategies from other similar reviews (30-34) of validation studies in EHR databases, were used to construct the search strategy for

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this review. To ensure the literature was comprehensively searched, reference lists from studies that were retrieved were also hand searched.

Study Selection Criteria

All studies validating definitions of AECOPD in EHRs were considered for inclusion in this review. Studies had to be written in English and published between 1946 (MEDLINE) or 1947 (Embase) and 31st May 2024.The specific criteria for inclusion were as follows:

- AECOPD admission data should come from either an EHR or an administrative claims database that routinely collect health data.
- The detection algorithms for AECOPD should be compared against a reference standard or gold standard definition (e.g. chart reviews or questionnaires completed by physicians to confirm and validate the diagnosis).
- Finally, a measure of validity should be available (e.g. sensitivity, specificity, PPV, NPV, and c-statistic, etc.) or there should be a means to calculate one from data within the study.

During the screening process, it became apparent that adding another criterion for inclusion was necessary: potential wider applicability of the algorithm (i.e. the algorithm could be applied to another dataset). As the aim of this review is to recommend algorithms for future research, it was therefore decided that studies should be excluded if they could not be easily applied to other datasets. Studies were also excluded if they only validated a diagnosis of COPD, not specifically an AECOPD.

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Data synthesis

The protocol for data management and synthesis is described by Stone et al.,(35). Two different reviewers (PS and EM) independently screened the articles selected for full text review and any disagreement between the reviewers were resolved by consensus or third reviewer (JKQ) arbitration. If studies were excluded the reasons were recorded, and the 2 reviewers extracted study details and assessed risk of bias for the included studies independently. Data were extracted into Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) and included:

- Details of the study (including title, first author name, year of publication, DOI)
- The aims of the study or research question
- Details of the EHR database
- A description of the studied population (specific groups, location and time period)
- A description of the AECOPD detection algorithm(s (e.g. the list of clinical codes used)
- Details of the reference standard or gold standard that the algorithm(s) were compared against
- The measure(s) of validity that were used (e.g. PPV, NPV etc) along with validity results
- The prevalence of AECOPD if available

The validity of the AECOPD detection algorithm was the primary outcome measure in this review.

The risk of bias in individual studies was assessed using a quality assessment tool for diagnostic accuracy studies known as the QUADAS-2 (36). The QUADAS-2 was specifically

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adapted to this review using the reporting checklist developed by Benchimol et al. (29) for use in validation studies of health administrative data. A copy of the adapted QUADAS-2 risk of bias assessment used in this study can be found in **Supplementary File 2**.

The registered protocol can be found on PROSPERO: International prospective register of systematic reviews (registration number: CRD42019130863) and has been published elsewhere (37).

Results

From the 2784 articles found by the search strategy,12 studies were eligible for inclusion and were included in the review (**Figure 1**). Six of the studies were in databases from the United States (US), four were from English national patient databases, one from a Japanese database and one came from the Danish National Patient Registry (summarised in **Table 1.** Full details of each study can be found in Supplementary File 3). The clinical terminology used to retrieve data on admissions was either ICD-9 (6 studies), ICD-10 (5 studies), or Read codes (2 studies by Rothnie et al.,(38, 39). Ages of patients varied between studies with one study using a broad definition of patients aged ≥18 years (40), whereas another study was more selective, including patients ≥55 years old (41). There was one conference abstract by Pu et al.,(42) that was included and it should be noted that it has not been through peer review, however sufficient detail was included in the abstract to allow for assessment in this review. For the reference standard, nine studies used chart review or consensus by physicians and nurses. One study by Rothnie et al., used a review of General Practitioner (GP) questionnaires (38) and a subsequent study by Rothnie et al., (39) utilised hospital discharge

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summaries. Finally, for their reference standard, Sperrin et al.,(43) compared the index test with AECOPD events recorded in clinical trial data.

Risk of bias assessment

The risk of bias for each study is shown in **Table 2**. None of the studies had a low risk of bias for all domains assessed. The reference standard was the domain in which studies struggled to score a low risk of bias. Only two out of the 12 studies scored low risk of bias for the reference standard (Mapel et al., (44) and Awano et al., (40)) and only three studies had a low risk of bias under applicability concerns because they used spirometry in the reference standard to confirm diagnosis of COPD (Thomsen et al.,(45), Echevarria et al.,(46), and Mapel et al.,(44)). The reference standard used by Thomsen et al.,(45) scored high risk of bias because physicians reviewing the charts were not blinded to the diagnosis codes of the index test, and therefore this could have influenced the interpretation and classification of the reference standard. This study was also at high risk of bias for flow and timing as it was unclear if all patients were included in the analysis as the busy hospitals (that may have had more severe cases) were unable to return all the details from the patient record. One other study (Sperrin et al., (43)) also had unclear risk of bias for the reference standard as it was unclear if results were interpreted without knowledge of the index test. In the Stein et al., (2012) study (47) patients that were transferred from another hospital were excluded and therefore this study scored unclear risk of bias for patient selection. The patients that were excluded may also have been more severe cases. The Rothnie et al., study (38) that validated primary care Read code definitions had high risk of applicability concerns because they compared the results of read code definitions against Hospital Episode Statistics (HES) ICD-10 code definitions (as the reference standard) and the results were not validated physicians (the gold standard). Finally, two studies scored high risk of bias for patient selection (Sperrin

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et al., (43) and Mapel et al., (44)) because they used more than one database to select patients from and this may have introduced bias as patients were not from one specific setting.

Summary of results for studies validating use of ICD-9 codes.

Studies validating ICD-9 codes **(Table 3)** were all carried out in the USA. All studies validated similar ICD-9 codes, and the single AECOPD code of 491.2x provided the best PPV in all studies, ranging between 60% and 100%. Ginde et al., (41) demonstrated high PPV (97%) for detection of AECOPD using three ICD-9-CM codes. However, results from Stein et al., (2010) (48) reported lower PPV values and these varied depending on which algorithm was used (74% for algorithm 1, 62% for algorithm 2, and 60% for algorithm 5), suggesting that the algorithms they used for identifying AECOPD may identify a substantial number of patients admitted for alternative conditions. A subsequent study by Stein et al., in 2012 (47) evaluated the 491.21 ICD-9 code in a comparison with other algorithms but found that sensitivity was reduced when using codes for a primary diagnosis of COPD (12.3%) or a secondary diagnosis of COPD with a primary diagnosis of respiratory failure (24.3%). Their results implied that ICD-9-CM codes may undercount hospitalizations for AECOPD and it is questionable whether researchers should rely on ICD-9-CM codes alone to identify AECOPD admissions. Pu et al.,(42) also validated the use of ICD-9 code 491.21 and found that using codes such as this could miss a significant proportion of patients with AECOPD. In a more recent study, Stanford et al., (49) modified the algorithm by Stein et al in 2012 (47) through the addition of further ICD-9 codes (493.12, 493.92, 494.1, 466.0) in order to identify exacerbation-related hospital visits and included events for which diagnosis codes may have been a primary or secondary diagnosis. The final algorithm in this study had a high sensitivity

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of 84.9% and PPV of 67.5%. Finally, a study in 2021 by Mapel et al., (44) developed two algorithms to identify moderate and severe COPD exacerbations. They used a broader algorithm using 18 different ICD-9 codes and required steroid or antibiotic prescription to identify moderate exacerbations. For severe exacerbations, the records required an inpatient hospital stay of 2 or more days plus one of 8 different ICD-9 codes. For both moderate and severe exacerbations the PPV was high (98.3% and 96.0% respectively).

Summary of results for studies validating ICD-10 codes

Of the studies using ICD-10 codes to identify AECOPD (**Table 4**), three were carried out in the UK (39, 43, 46) and one was carried out in Japan (40). All studies validated variations of J44 COPD codes, except for Awano et al.,(40) who validated a broader collection of ICD-10 codes (J410, J411, J42, J43, J44, J449, J841). Specificity and NPV were high in this study (96.1% and 82.9% respectively), however sensitivity was low (33.7%). In the Danish study (45), J44 was used as a parent code for primary AECOPD diagnosis resulting in the best PPV (93%), and when testing all three algorithms good PPVs were found. In the UK, Rothnie et al., (39) the highest sensitivity (87.5%) was found using a COPD code (J44.9) as the primary diagnosis, or using codes for AECOPD (J44.0 or J44.1) or lower respiratory tract infections (LRTI) (J22) as either primary or secondary diagnosis codes. The high sensitivity found with this algorithm by from Rothnie et al., (39) may represent a good compromise between high sensitivity and high PPV because it is similar to the algorithm by Thomsen et al., (45) which gave a high PPV. In a more recent UK study, Sperrin et al.,(43) used algorithms for read codes and ICD-10 codes from both Rothnie et al., studies (38, 39). Results were populated from a best-case scenario, using the full algorithm in primary and secondary care, and allowing a maximum gap in the start or end dates of the episodes of up to 15 days. This gave a PPV of 73.6% and a sensitivity of 69.1%. Finally, Echevarria et al.(46), also in the UK

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

using J44 ICD-10 codes alone, reported a PPV of 63.9%, NPV of 75.5%, sensitivity of 70.7% and specificity of 69.4%.

Summary of results for studies validating Read codes

Two studies validating the use of Read codes were done in the UK by Rothnie et al., in 2016 (38, 39) (**Table 5**). The first Rothnie et al., study validated the use of Read codes in English primary care against a reference standard of GP questionnaires (38). PPV and sensitivity were used to validate the algorithms and the best compromise was found between the two measures when combining their algorithms with a PPV >75%. Using the same definitions as the first, the second study validated the algorithms against HES ICD-10 codes.(39) The combination in the algorithm included antibiotic and oral corticosteroid prescription for 5-14 days, a symptom (such as dyspnoea, cough, or sputum) in addition to the prescription of antibiotics or oral corticosteroids, a LRTI, or an AECOPD code, and produced a PPV of 85.5% and sensitivity of 62.9%.

A quantitative synthesis was unfortunately not possible because the limited number of studies in which the same clinical terminology was used, and a lack of data on true and false positives and negatives.

Discussion

This systematic review assessed different methods for validating the recording of acute exacerbations of COPD in electronic health records and found that a variety of definitions were used. Studies used ICD-9 codes, ICD-10 codes and different combinations of clinical codes in both primary care (using Read codes) and secondary care settings.

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Results from studies validating ICD-9 codes suggest that ICD-9 codes alone may not accurately identify all patients with AECOPD. The validation measurements varied considerably depending on which codes or algorithms were used. The code 491.21 is used to classify obstructive chronic bronchitis with acute exacerbation and this code had high PPV of 100% in one study (41) but had low sensitivity in other studies (42, 47) suggesting that ICD-9 codes alone may underestimate the burden of hospitalizations for COPD. Other studies (49) modified their algorithms through the addition of further ICD-9 codes, for example using those to denote asthma with acute exacerbation, bronchiectasis, and acute bronchitis. Although this improved the sensitivity of the algorithm (84.9%), the ability to detect true positives was not as high (PPV 67.5%). However, using multiple ICD-9 codes alongside additional information on treatment from care records such as the prescription of steroids or antibiotics, gave high PPVs for moderate (98.3%) and severe (96.0%) AECOPD in another study (44).

Our review also found that, as with ICD-9 codes, using ICD-10 codes alone in the algorithms may not effectively identify admissions for AECOPD in EHRs. In the UK, Echevarria et al.,(46) found that using ICD-10 codes alone missed almost a third of patients admitted with AECOPD in their study. By contrast, the Danish study (45) found that using a J44 parent code as primary diagnosis gave a high PPV (93%). However, in this study the reviewers were not blinded to the diagnosis codes and therefore knowledge of this could have influenced results of the physician's assessment. The recent study in a Japanese database (DPC) (40) combined multiple ICD-10 codes in addition to J44, including those for bronchitis (J40, J411, J42), emphysema (J43), and acute interstitial pneumonitis (J841). Although the specificity and NPV were high (96% and 83% respectively), sensitivity was low (34%). The authors presumed that diagnoses for chronic diseases such as COPD had not been recorded in the

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DPC database as specific tests or treatments were not required during hospitalization. This suggests the use of other clinical data in addition to ICD-10 codes would improve identification of hospitalizations for AECOPD. Rothnie et al., completed two studies in 2016 validating the recording of AECOPD cases within UK health records. In the first study (38), the data collected was purely from primary healthcare via the CPRD database using Read codes and product codes. It was suggested that using multiple codes increased the validity, in this case AECOPD, lower respiratory tract infection codes, antibiotics and oral corticosteroid codes were utilised. This combination of codes led to a PPV of 85.5% but a lower sensitivity of 62.9%, suggesting that although the strategy was valid it would underestimate the number of events. The second study (39) then aimed to identify hospitalizations for AECOPD in CPRD using secondary care data linked to HES and found a sensitivity of 87.5%. However, when using a code suggesting hospitalization for AECOPD in primary care data alone without HES linkage, a much lower PPV of 50.2% and a sensitivity of 4.1% was found. This implies that Primary care data alone does not accurately identify hospitalizations for AECOPD, and researchers should use primary care data that are linked to data from secondary care.

As the screening process was undertaken, it became clear that one study by Shah et al.,(50) stood out for using very different algorithms to the other studies. For the index test they compared 6 models with different combinations of clinical and administrative data detailing care steps for patients admitted to hospital including COPD “power plans”, bronchodilator protocol use, billing diagnosis and treatments administered such as steroid use and oxygen management. And unlike other studies in which ICD-10 codes were used as the index test, this study used the final billing ICD-10 diagnosis for AECOPD as the reference standard for comparing model performance. Since the aim of this review is to provide guidance on which

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

algorithms provide the most accurate cohort of AECOPD, it became apparent that researchers should be able to apply the recommended algorithms to other datasets, and therefore our additional exclusion criteria ruled out this study from our review.

None of the studies had a low risk of bias for all domains assessed meaning that validity of all the studies may be overestimated. Most studies scored high risk of bias for applicability of the reference standard because they did not use spirometry to confirm COPD diagnosis. Spirometry is a key component of COPD diagnosis and therefore not including it to confirm COPD in the reference standard could increase the risk of bias. Stein et al., 2012 (47) explained the reason why they deliberately did not confirm COPD diagnosis in their reference standard with spirometry as *"it would have led to a narrowly selected (and potentially biased) sample with which to evaluate the validity of ICD-9-CM algorithms."* In this case, the authors were aiming for sensitivity over specificity. However, their definition should still be considered at risk of bias because it makes more likely the reference standard could include non-COPD cases.

A similar systematic review was conducted looking at validation of codes for asthma within EHRs (30).They conducted a search and found 13 studies that fit their inclusion criteria, particularly choosing to focus on the databases and codes used, along with any sensitivity or specificity measures. As in our review in which the validity of definitions of AECOPD varied across different database and settings, they found that case definitions and methods of asthma diagnosis validation also varied widely across different EHR databases. The authors suggested that the source of the EHR databases (primary care, secondary care, and urgent care) could influence the case definition of asthma and the way the validation is conducted. For example, patients seeking care for asthma symptoms might present differently in each setting, and the test measures therefore might reflect this.

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

In this study we have found that using single codes to search for case definitions of AECOPD in EHR may not effectively identify admissions for AECOPD. Some of the research has shown that modifying algorithms with additional codes may improve sensitivity but at the expense of accurately identifying true positives. This review and others (26, 30) have shown that different research questions may necessitate different case definitions, for example if researchers want to prioritise specificity over sensitivity, a more restrictive definition of AECOPD would be used, and vice versa. The Stein et al., (2010) (48) findings suggested that the selection of an algorithm should depend on its intended purpose. For example, if the intent is to identify patients for quality measurement, an algorithm with the highest PPV would be desirable (e.g. their first algorithm using ICD-9 code 491.21). However, if the intent is to estimate the overall burden of disease, then the authors suggested using a more inclusive approach. We propose that a Delphi study would be useful to obtain the consensus of expert clinicians and researchers to decide which algorithms would be recommended in different research scenarios.

There are some strengths and limitations to our study. To our knowledge this is the first review to systematically review studies that validated definitions of AECOPD in electronic health records. We used broad search criteria which meant that we could review a variety of different codes and algorithms used in different databases globally. However, we found that in many studies, the clinical codes utilised were not well reported or were difficult to obtain. Our risk of bias assessment, the adapted QUADAS-2, may have unfairly scored studies that did not use spirometry in the reference standard with a high risk of bias because spirometry was unavailable to confirm diagnosis of COPD. However, this highlights the importance and need for spirometry data in EHRs. Finally, we were unable to carry out a quantitative analysis because of the limited number of studies included in our review.

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COPD and acute exacerbations are underdiagnosed in the general population (51) and this is related to underuse of spirometry as we found in many of the studies. Furthermore, recordings of acute exacerbations of COPD in EHR tend to capture events that lead to healthcare utilization, such as moderate and severe exacerbations, therefore limiting the capture of mild exacerbations. These are important points for researchers to consider in future when devising methods to identify AECOPD in EHR, and to find ways of balancing sensitivity versus specificity.

Conclusion

The methods used for validating definitions of acute exacerbations of COPD in electronic healthcare vary, with different algorithms and case definitions used in different databases globally and in different settings such as primary and secondary care. Using single codes to identify COPD exacerbations (for example ICD-9 code 491.21 or ICD-10 code J44) were found to have a high PPV in some studies but low sensitivity in others. This means that the algorithms used can positively identify cases of AECOPD within datasets but may not accurately identify all cases. At present, there is no clear consensus on which definition provides the highest validity or the most sensitive and specific results when searching EHRs for AECOPD cases. The variation between studies in defining COPD exacerbations restricts the ability of researchers to reliably compare findings and provide robust evidence. Consensus from experts is required to guide researchers on which definitions to use in different research scenarios. Researchers should endeavour to make all their disease definitions easily accessible so that others can validate and replicate them.

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Author Contributions

JKQ, EM and PS were responsible for conception and design of the work. All authors were responsible for the acquisition of data, data analysis and interpretation. EM and PS were equally responsible for writing the manuscript. In addition, all authors have read and approved of the manuscript.

Declaration of Interests

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Table 1. Summary of studies included

Author, year, country, period	Population characteristics	Data source	Code type	Reference Standard
Ginde et al., 2008 (41), USA, July 2005 – June 2006	Patients ≥55 years visiting emergency department	Unspecified EHR database from two US hospitals	ICD-9-CM	Chart review by 2 physicians
Stein et al., 2010,(48) USA, 2000 – 2006	Patients ≥40 years with ICD-9-CM code for AECOPD	National Inpatient Sample (NIS)	ICD-9-CM	Chart abstracted physician diagnosis
Thomsen et al., 2011 (45), Denmark, January 2008 – December 2008	Patients ≥30 years with hospital discharge diagnosis for COPD	Danish National Patient Registry (DNPR) discharge codes from 34 Danish hospitals	ICD-10	Physician review of patient medical records.
Stein et al., 2012 (47), USA, November 2005 – October 2006	Patients ≥ 40 years with hospital admission	Discharge codes from 2 hospitals in Chicago, USA	ICD-9-CM	Physician chart abstraction

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Rothnie et al., 2016 (38), UK, January 2004 – August 2013	COPD patients ≥35 years with additional material provided by GP	Clinical Practice Research Datalink (CPRD)	Read and Product codes	Review of GP questionnaires by 2 physicians
Rothnie et al., 2016 (39), UK, January 2004 – March 2014	COPD patients ≥35 years COPD patients ≥35 years	Hospital Episodes Statistics (HES) CPRD	ICD-10 Read and Product Codes	Hospital discharge summaries (HES-recorded hospitalization for AECOPD)
Pu et al., 2017 (42), USA, 2012 – 2014	Patients discharged with ICD-9 code for AECOPD	Hospital database	ICD-9	Chart review
Sperrin et al., 2019 (43) UK, March 2012-October 2014	Patients ≥40 years who had received a documented diagnosis of COPD from a GP and recorded one or more COPD exacerbations in the previous 3 years	Electronic Health Records and electronic case report forms in the Salford Lung Study	Read version 2 or ICD-10 codes.	AECOPD events recorded in clinical trial
Echevarria et al., 2020 (46) UK,	Patients admitted to hospital identified with AECOPD.	Hospital discharge codes	ICD-10 codes	Consensus of 2 respiratory specialists

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

January 2012 – May 2013				using GOLD guidelines
Stanford et al., 2020 (49) USA, January 2009 – December 2013	Patients ≥ 40 years with ICD-9-CM codes for COPD	US healthcare-claims database – Optum Research Database	ICD-9-CM	Review of medical records by physician
Mapel et al., 2021 (44) USA, January 2010 – September 2015.	Patients aged ≥ 40 years with ≥ 1 hospitalization, ≥ 1 emergency department visit, or ≥ 2 outpatient visits with a primary or secondary COPD diagnosis	Two independent EHR systems: Kaiser Permanente Mid-Atlantic States (KPMAS) and Reliant Medical Group, Inc. (Reliant).	ICD-9-CM	Chart review by pulmonary nurses using GOLD guidelines
Awano et al., 2023 (40) Japan, April 2019 – March 2021	Patients ≥ 18 years hospitalized in 2 acute-care hospitals in Tokyo.	Diagnosis Procedure Combination (DPC) database	ICD-10 codes	Physician review of medical records

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Table 2. Adapted QUADAS-2 risk of bias results table for studies included

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Ginde et al., 2008 (41)	□	□	?	□	□	□	□
Stein et al., 2010 (48)	□	□	?	□	□	□	□
Thomsen et al., 2011 (45)	□	□	□	□	?	□	□
Stein et al., 2012 (47)	?	□	□	□	□	□	□
Rothnie et al., 2016 (38) Read codes	□	□	?	□	□	□	□
Rothnie et al., 2016 (39)	□	□	?	□	□	□	□

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

(HES/ICD-10)							
Pu et al., 2017 (42)	?	□	?	?	?	□	□
Sperrin et al., 2019 (43)	□	□	?	□	□	□	□
Echevarria et al., 2020 (46)	□	□	?	□	?	□	□
Stanford et al., 2020 (49)	□	□	?	□	□	□	□
Mapel et al., 2021 (44)	□	□	□	?	□	□	□
Awano et al., 2023 (40)	□	□	□	□	?	□	□

□ = Low risk of bias □ = High risk of bias ? = Unclear risk of bias

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Table 3. Summary of ICD-9 validation studies of AECOPD definitions

Study	Algorithm (codes)	Gold standard reference	N	PPV / Derived PPV (95% CI)	NPV / Derived NPV (95% CI)	Sensitivity / Derived Sensitivity (95% CI)	Specificity / Derived Sensitivity (95% CI)
Ginde et al., 2008 (41)	491.2x	Consensus by two emergency physicians from abstracted chart data	181	100% (98-100)	-	-	-
	491.2x, 492.8, or 496	"	200	97% (93-99)	-	-	-
Stein et al., 2010(48)	Algorithm 1: 491.21 primary diagnosis	Primary diagnosis recorded in physician notes	Sample of 200	74%	-	-	-
	Algorithm 2: 491.x, 492.x, or 496	"		62%	-	-	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

	Algorithm 5: 491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, or 496 primary diagnosis OR 518.81, 518.82, or 518.84 primary diagnosis AND 491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, or 496 secondary diagnosis	”		60%	-	-	-
Stein et al., 2012 (47)	Primary diagnosis of COPD (491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, 496) OR primary diagnosis of respiratory failure (518.81, 518.82, 518.84) AND secondary diagnosis of COPD (defined using same	Physician chart abstraction: physician diagnosis of COPD; presence of cough, dyspnoea, or sputum production on presentation; and	46	85.4%	93.9%	24.3%	99.7%

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

	codes as primary diagnosis) (age >=40)	hospitalisation for one of these respiratory symptoms					
	Primary diagnosis of AECOPD: 491.21 (age>=40)	”	20	97.2%	93%	12.3%	100%
Pu et al., 2017 (42)	491.21 (AECOPD)	Chart review	620	91% (88-93)	31% (27-35)	57% (54-61)	76% (70-81)
Stanford et al., 2020 (49)	Claims based algorithm (modified from the Stein 2012 algorithm through the addition of further ICD-9 codes - 493.12, 493.92, 494.1, 466.0)	Review of exacerbation history in medical records by patient’s physician.	402	67.5%	-	84.90%	-
Mapel et al., 2021 (44)		Chart review by trained pulmonary nurses using	298	98.3% (96.1–99.5)	75.0% (65.3, 83.1)	-	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

		GOLD COPD 2017 definition.					
	Severe exacerbations: At least 1 inpatient hospital stay or 2 or more days with any of the following ICD-9-CM codes as primary diagnosis: 491, 492, 493.20, 493.22, 496, 518.81, 518.82, 518.84.	”	225	96.0% (92.5–98.2)	95.0% (88.7, 98.4)	-	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Table 4. Summary of ICD-10 validation studies of AECOPD definitions

Study	Algorithm(s)	Gold standard reference	N	PPV / Derived PPV (95% CI)	NPV / Derived NPV (95% CI)	Sensitivity / Derived Sensitivity (95% CI)	Specificity / Derived Sensitivity (95% CI)
Thomsen et al., 2011 (45)	J44 (COPD) as primary diagnosis	Physician review of patient medical records	1223	93% (92-95)	-	-	-
	Pneumonia (J13-J18) without J44		1432	-	82% (80-84)	-	-
Rothnie et al., 2016 (39) (HES/ICD-10)	Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any position or COPD code (J44.9) in the first position in any FCE during spell	Hospital discharge summary	40	-	-	87.5% (72.4-94.9)	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Sperrin et al., 2019 (43)	Algorithms for both **read codes from Rothnie et al., 2016 (38) AND ICD-10 codes from Rothnie et al.,(39)** Results from a '*best-case scenario'*, using the full algorithm in primary and secondary care, and allowing a maximum gap in the start or end dates of the episodes of up to 15 days	Moderate and severe AECOPD episodes reported in the eCRF for a clinical trial	3,042	73.6%	-	69.1%	-
Echevarria et al., 2020 (46)	COPD codes J44	Consensus of 2 respiratory specialists using GOLD guidelines	1,014	63.9%	75.5%	70.7%	69.4%

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Awano et al., 2023 (40)	COPD codes J410, J411, J42, J43, J44, J449, J841	Physician review of patient medical records	92	72.1%	82.9%	33.7%	96.1%

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Table 5. Summary of Read code validation studies of AECOPD

Study	Algorithm(s)	Gold standard reference	N	PPV / Derived PPV (95% CI)	NPV / Derived NPV (95% CI)	Sensitivity / Derived Sensitivity (95% CI)	Specificity / Derived Sensitivity (95% CI)
Rothnie et al., 2016 (38) (subset with additional patient data)	Oral corticosteroid (OCS) prescription	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)	367	72.2% (66.5-77.9)	-	22.7% (16.1-29.2)	-
	Antibiotic prescription		2245	61.3% (58.3-64.3)	-	63.4% (55.4-71.4)	-
	Lower respiratory tract infection (LTRI) code and OCS (on the same day)		621	84.5% (80.6-88.5)	-	20.6% (15.2-26.0)	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

	AECOPD code		350	98.3% (96.9-99.6)	-	26.8% (19.7-33.9)	-
Rothnie et al., 2016 (38) (subset with additional patient data - combined algorithms)	Prescription of antibiotics and OCS for 5-14 days; or Symptom definition with prescription of antibiotic or OCS; or LRTI code; or AECOPD code	Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)		85.5% (82.7-88.3)	-	62.9% (55.4-70.4)	-
	All algorithms combined			63.8% (61.0-66.6)	-	88.1% (82.9-93.4)	-
Rothnie et al., 2016 (39) (CPRD/Read)	AECOPD hospitalisation code	HES: Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any		50.2% (48.5-51.8)	-	4.1% (3.9-4.3)	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

	AECOPD identified using validated algorithm and hospitalisation code	position or COPD code (J44.9) in the first position in any FCE during spell		43.3% (42.3-44.2)	-	5.4% (5.1-5.7)	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

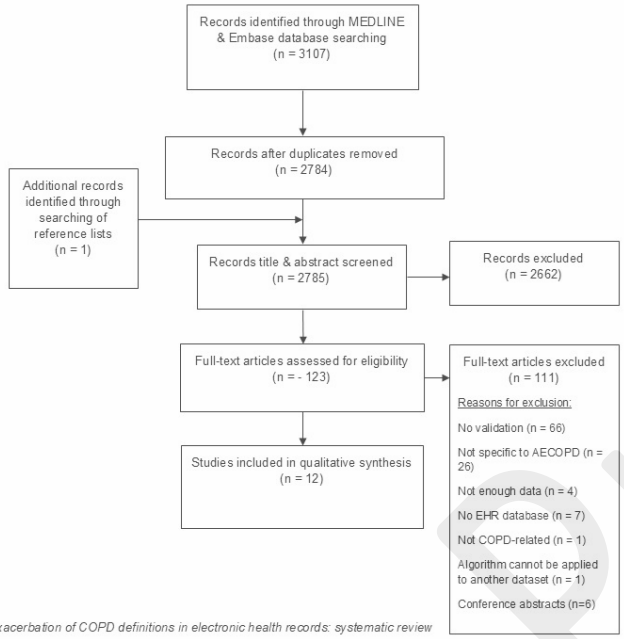

Figure 1. *PRISMA flowchart for validation of acute exacerbation of COPD definitions in electronic health records: systematic review*

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Online Supplement

Supplementary File 1

Medline search strategy

1. lung diseases, obstructive/ or exp bronchitis/ or exp pulmonary disease, chronic obstructive/

2. (COPD or COAD or emphysema or chronic bronchitis).ab,kf,ti.

3. (chronic obstructive adj (pulmonary or lung or airway$ or airflow) adj disease).ab,kf,ti.

4. 1 or 2 or 3

5. clinical deterioration/

6. (exacerbation$ or hospital$).ab,kf,ti.

7. 5 or 6

8. 4 and 7

9. (AECOPD or ECOPD or AECB).ab,kf,ti.

10. 8 or 9

11. database management systems/ or electronic data processing/ or exp health information management/ or databases as topic/ or databases, factual/ or health information systems/ or consumer health informatics/ or medical informatics/ or health information exchange/ or medical informatics applications/ or medical informatics computing/ or public health informatics/

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12. medical records/ or health records, personal/ or patient generated health data/ or medical record linkage/ or medical records, problem-oriented/ or medical records systems, computerized/ or electronic health records/ or registries/

13. Clinical Coding/ or current procedural terminology/ or healthcare common procedure coding system/ or "international classification of diseases"/ or "logical observation identifiers names and codes"/ or rxnorm/ or "systematized nomenclature of medicine"/

14. (EHR$1 or EMR$1 or electronic health record$1 or electronic medical record$1).ab,kf,ti.

15. ((billing or claim$ or admin$ or utili?ation or patient or inpatient or in-patient or outpatient or out-patient or care or medical or clinical or health$ or hospital$ or electronic or digit$ or computer$) adj2 (data$ or record$1 or system$1)).ab,kf,ti.

16. (billing code or discharge code or Read code or SNOMED CT or ICD*).ab,kf,ti.

17. 11 or 12 or 13 or 14 or 15 or 16

18. Validation Studies as Topic/ or Validation Studies/

19. "sensitivity and specificity"/ or "predictive value of tests"/ or roc curve/

20. (validation or validity or verification or verify or identification or identify).ab,kf,ti.

21. ((case or cases) adj2 (definition$ or define$ or evaluat$)).ab,kf,ti.

22. (sensitivity or specificity or PPV or PNV or NPV or positive predictive value$ or predictive positive value$ or predictive negative value$ or negative predictive value$ or likelihood ratio or precision or accuracy or ROC or receiver operating characteristic$ or kappa or "c-statistic" or (concordance adj statistic) or "c-index").ab,kf,ti.

23. 18 or 19 or 20 or 21 or 22

24. 10 and 17 and 23

Embase Search Strategy

1. exp chronic obstructive lung disease/

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2. emphysema/

3. exp chronic bronchitis/

4. (COPD or COAD or emphysema or chronic bronchitis).ab,kw,ti.

5. (chronic obstructive adj (pulmonary or lung or airway$ or airflow) adj disease).ab,kw,ti.

6. 1 or 2 or 3 or 4 or 5

7. exp disease exacerbation/

8. hospitalization/

9. (exacerbation$ or hospital$).ab,kw,ti.

10. 7 or 8 or 9

11. 6 and 10

12. (AECOPD or ECOPD or AECB).ab,kw,ti.

13. 11 or 12

14. data base/

15. medical informatics/ or medical information system/

16. exp medical record/ or electronic health record/ or electronic medical record/ or electronic medical record system/ or electronic patient record/ or register/

17. Current Procedural Terminology/ or coding/

18. exp "international classification of diseases"/ or "Systematized Nomenclature of Medicine"/ or "logical observation identifiers names and codes"/

19. (EHR$1 or EMR$1 or electronic health record$1 or electronic medical record$1).ab,kw,ti.

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

20. ((billing or claim$ or admin$ or utili?ation or patient or inpatient or in-patient or outpatient or out-patient or care or medical or clinical or health$ or hospital$ or electronic or digit$ or computer$) adj2 (data$ or record$1 or system$1)).ab,kw,ti.

21. (billing code or discharge code or Read code or SNOMED CT or ICD*).ab,kw,ti.

22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23. validation study/

24. "sensitivity and specificity"/ or predictive value/ or receiver operating characteristic/

25. (validation or validity or verification or verify or identification or identify).ab,kw,ti.

26. ((case or cases) adj2 (definition$ or define$ or evaluat$)).ab,kw,ti.

27. (sensitivity or specificity or PPV or PNV or NPV or positive predictive value$ or predictive positive value$ or predictive negative value$ or negative predictive value$ or likelihood ratio or precision or accuracy or ROC or receiver operating characteristic$ or kappa or "c-statistic" or (concordance adj statistic) or "c-index").ab,kw,ti.

28. 23 or 24 or 25 or 26 or 27

29. 13 and 22 and 28

Supplementary File 2

Moore E et al

QUADAS-2 (adapted for validation of AECOPD recording in healthcare databases review)

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Domain 1: Patient selection

A. Risk of bias

Describe methods for patient selection:

• Was a consecutive or random sample of patients enrolled? YES/NO/UNCLEAR

• Was a case-control design avoided? YES/NO/UNCLEAR

• Did the study avoid inappropriate exclusions? YES/NO/UNCLEAR

Could the patient selection have introduced bias? RISK: HIGH/LOW/UNCLEAR

(Score low if answers to all signalling questions were yes. Score high if any answers were no. Score unclear if any were answered as unclear with remainder scoring low)

B. Concerns regarding applicability

Describe included patients:

• Were patients from a single EHR database that comprised patients from one specific setting (e.g. primary or secondary care only patients)? YES/NO/ UNCLEAR

• Were patients aged 35 years or more with a recorded diagnosis of COPD? YES/NO/UNCLEAR

Is there concern that the included patients do not match the review question?

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CONCERN: HIGH/LOW/UNCLEAR

(*Score low answered yes to both questions. Score high if no to both questions. Score unclear if one marked as unclear.)*

Domain 2: Index test(s)

A. Risk of bias

Describe the index test and how it was conducted and interpreted:

• Was the AECOPD detection algorithm designed without knowledge of the result of the

reference standard (in the final validated population)? YES/NO/UNCLEAR

Could the interpretation of the index test have introduced bias?

RISK: HIGH/LOW/UNCLEAR

(Score low if all answers to signalling questions were yes. Score high if any were answered no. Score unclear if any were answered as unclear with remainder scoring low).

B. Concerns regarding applicability

• Were specific clinical codes / algorithms used to identify patients (i.e. a free text search wasn't used as part of patient identification)? YES/NO

Is there concern that the index test, its conduct or interpretation differ from the review question? CONCERN: HIGH/LOW/UNCLEAR

(Score low if clear descriptions of clinical codes/algorithms were given to identify patients.)

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Domain 3: Reference standard

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted:

• Is the reference standard likely to correctly classify the target condition?

YES/NO/UNCLEAR

• Were the reference standard results interpreted without knowledge of the index test?

YES/NO/UNCLEAR

Could the reference standard, its conduct, or its interpretation have introduced bias?

RISK: HIGH/LOW/UNCLEAR

(Score low if all answers to signalling questions were yes. Score high if any were answered no. Score unclear if any were answered as unclear with remainder scoring low)

B. Concerns regarding applicability

• Was there a diagnosis of COPD confirmed using spirometry? YES/NO/UNCLEAR

• Was diagnosis confirmed by a physician reviewing the patient's medical record?

YES/NO/UNCLEAR

• Did more than one physician review the medical record to confirm diagnosis and was

there strong agreement between the reviewing physicians? YES/NO/UNCLEAR

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: HIGH/LOW/UNCLEAR

(Score low if all answers to signalling questions were yes. Score high if any were answered no. Score unclear if any were answered unclear with the remainder low).

Domain 4: Flow and timing

A. Risk of bias

- Did all patients receive a reference standard? YES/NO/UNCLEAR
- Did patients receive the same reference standard? YES/NO/UNCLEAR
- Were all patients included in the analysis? YES/NO/UNCLEAR

Could the patient flow have introduced bias? RISK: HIGH/LOW/UNCLEAR

(Score low if all answers to signalling questions were yes. Score high if any answers were no. Score unclear if any were answered as unclear with the remainder scoring low).

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Table 6. Detailed Summary of ICD-9 validation studies of AECOPD definitions

Study	***Algorithm (codes)***	***Gold standard reference***	***N***	***PPV / Derived PPV (95% CI)***	***NPV / Derived NPV (95% CI)***	***Sensitivity / Derived Sensitivity (95% CI)***	***Specificity / Derived Sensitivity (95% CI)***
Ginde et al., 2008 *(41)* *Median age = 71* *Retrospective cohort study. 2 emergency departments.*	*491.2x*	*Consensus by two emergency physicians from abstracted chart data*	*181*	*100% (98-100)*	-	-	-
	492.8	*Consensus by two emergency physicians from abstracted chart data*	*4*	*75% (19-99)*	-	-	-
	496	*Consensus by two emergency physicians*	*15*	*60% (32-84)*	-	-	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

		from abstracted chart data					
	491.2x, 492.8, or 496	*Consensus by two emergency physicians from abstracted chart data*	*200*	*97% (93-99)*	-	-	-
Stein et al., 2010(48) *Mean age:* *Algorithm 1 = 69.4* *Algorithm 2 =* *69.5* *Algorithm 5 = 68.8* *Nationwide Inpatient Sample in US.*	*Algorithm 1: 491.21 (Obstructive chronic bronchitis with acute exacerbation) primary diagnosis*	*Primary diagnosis recorded in physician notes*	*Sample of 200*	*74%*	-	-	-
	Algorithm 2: 491.x, 492.x, or 496 (Chronic airway obstruction, not elsewhere classified) primary diagnosis	*Primary diagnosis recorded in physician notes*		*62%*	-	-	-
	Algorithm 5: 491.0 (Simple chronic bronchitis), 491.1 (Mucopurulent chronic bronchitis), 491.21 (Obstructive chronic bronchitis with acute exacerbation), 491.22 (Obstructive chronic bronchitis with acute exacerbation), 491.8 (Other chronic bronchitis), 491.9 (Unspecified chronic bronchitis),	*Primary diagnosis recorded in physician notes*		*60%*	-	-	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

	492.0 (Emphysematous bleb), 492.8 (Other emphysema), 493.22 (Chronic obstructive asthma with acute exacerbation), or 496 (Chronic airway obstruction, not elsewhere classified) primary diagnosis OR 518.81 (Acute respiratory failure), 518.82 (Other pulmonary insufficiency not elsewhere classified), or 518.84 (Acute and chronic respiratory failure) primary diagnosis AND 491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, or 496 secondary diagnosis						
***Stein et al., 2012** (47)* *Mean age = 56.1.* *2 urban academic*	*Primary diagnosis of COPD (490, 491.x, 492.x, 493.22, 496) OR primary diagnosis of respiratory failure (518.81, 518.82, 518.84, 799.1) AND secondary diagnosis of COPD (defined using same codes as primary diagnosis) (age >=25)*	*Physician chart abstraction: physician diagnosis of COPD; presence of cough, dyspnoea, or sputum production on presentation; and hospitalisation for one of*	*50*	*81.2%*	*93.9%*	*24.7%*	*99.5%*

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

medical centres in US.		*these respiratory symptoms*					
	Primary diagnosis of COPD (491.0, 491.1, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.22, 496) OR primary diagnosis of respiratory failure (518.81, 518.82, 518.84) AND secondary diagnosis of COPD (defined using same codes as primary diagnosis) (age >=40)	*Physician chart abstraction: physician diagnosis of COPD; presence of cough, dyspnoea, or sputum production on presentation; and hospitalisation for one of these respiratory symptoms*	*46*	*85.4%*	*93.9%*	*24.3%*	*99.7%*
	Primary diagnosis of COPD: 491.x, 492.x, 496 (age>=40)	*Physician chart abstraction: physician diagnosis of COPD; presence of cough, dyspnoea, or sputum production on presentation; and hospitalisation for one of these respiratory symptoms*	*29*	*85.6%*	*93.2%*	*14.5%*	*99.8%*
	Primary diagnosis of AECOPD: 491.21 (age>=40)	*Physician chart abstraction: physician diagnosis of COPD;*	*20*	*97.2%*	*93%*	*12.3%*	*100%*

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

		presence of cough, dyspnoea, or sputum production on presentation; and hospitalisation for one of these respiratory symptoms					
Pu et al., 2017 (42) *Mean age = 60.* *Hospital database in US.*	*491.21 (AECOPD)*	*Chart review*	*620*	*91% (88-93)*	*31% (27-35)*	*57% (54-61)*	*76% (70-81)*
Stanford et al., 2020 (49) *Mean age = 67.6* *US healthcare claims database.*	*Claims based algorithm (modified from the Stein 2012 algorithm through the addition of further ICD-9 codes - 493.12, 493.92, 494.1, 466.0)*	*Review of exacerbation history in medical records by patient's physician.*	*402*	*67.5%*	-	*84.90%*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Mapel et al., 2021 (44) *Mean age:* *Reliant = 72.7* *KPMAS = 68.9*	***Moderate exacerbations**: At least 1 office or outpatient non-emergency department visit with any of the following ICD-9-CM codes as the primary diagnosis:* *466,486,490, 491, 492.xx, 493.20, 493.22, 493.92, 496, 518.81, 518.82, 518.84, 786.0, 786.05, 786.2, 786.5, 786.07, 799.0.* ***AND*** *at least 1 associated pharmacy dispensing for theophylline (intravenous) or aminophylline (intravenous) or systemic steroids or any of the following antibiotics (amoxicillin, beta-lactamase inhibitor, 2nd to 4th generation cephalosporins, macrolides or doxycycline).*	*Chart review by trained pulmonary nurses using GOLD COPD 2017 definition.*	*298*	*98.3% (96.1–99.5)*	*75.0% (65.3, 83.1)*	-	-
	***Severe exacerbations:** At least 1 inpatient hospital stay or 2 or more days with any of the following ICD-9-CM codes as primary diagnosis:* *491, 492, 493.20, 493.22, 496, 518.81, 518.82, 518.84.*	*Chart review by trained pulmonary nurses using GOLD COPD 2017 definition.*	*225*	*96.0% (92.5–98.2)*	*95.0% (88.7, 98.4)*	-	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

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Table 7. Detailed summary of ICD-10 validation studies of AECOPD definitions

Study	***Algorithm(s)***	***Gold standard reference***	***N***	***PPV / Derived PPV (95% CI)***	***NPV / Derived NPV (95% CI)***	***Sensitivity / Derived Sensitivity (95% CI)***	***Specificity / Derived Sensitivity (95% CI)***
Thomsen et al., 2011 (45) *Median age = 74* *Danish National Patient Registry (DNPR)*	*PPV: J44 (COPD) primary or secondary diagnosis*	*Physician review of patient medical records*	*1581*	*92% (91-93)*	-	-	-
	PPV: J44 (COPD) as primary diagnosis	*Physician review of patient medical records*	*1223*	*93% (92-95)*	-	-	-
	PPV: J44 (COPD) as secondary diagnosis, acute respiratory failure or pneumonia as primary diagnosis	*Physician review of patient medical records*	*358*	*87% (84-91)*	-	-	-
	NPV: Pneumonia (J13-J18) or acute respiratory failure (J96) without J44	*Physician review of patient medical records*	*1546*	-	*81% (79-83)*	-	-
	NPV: Pneumonia (J13-J18) without J44	*Physician review of patient medical records*	*1432*	-	*82% (80-84)*	-	-
	NPV: Acute respiratory failure (J96) without J44	*Physician review of patient medical records*	*114*	-	*59% (49-68)*	-	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Rothnie et al., 2016 (39) (HES/ICD-10) *Age (%)* *65-74 = 31.4%* *≥75 = 21.7%*	*Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any position or COPD code (J44.9) in the first position in any FCE during spell*	*Hospital discharge summary*	*40*	-	-	*87.5% (72.4-94.9)*	-
	Specific AECOPD code (J44.0 or J44.1) or COPD code (J44.9) in any position in any FCE during spell	*Hospital discharge summary*	*40*	-	-	*85.0% (69.6-93.3)*	-
	Specific AECOPD code (J44.0 or J44.1) in any position or LRTI code (J22) or COPD code (J44.9) in the first position in any FCE during spell	*Hospital discharge summary*	*40*	-	-	*85.0% (69.6-93.3)*	-
	Specific AECOPD code (J44.0 or J44.1) in any position or COPD code (J44.9) in the first position in any FCE during spell	*Hospital discharge summary*	*40*	-	-	*77.5% (61.3-88.2)*	-
	Specific AECOPD code (J44.0 or J44.1) in any position in any FCE during spell	*Hospital discharge summary*	*40*	-	-	*77.5% (61.3-88.2)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

	Specific AECOPD code (J44.0 or J44.1) in the first position in first FCE during spell	*Hospital discharge summary*	*40*	-	-	*65.0% (48.5-78.6)*	-
Sperrin et al., 2019 (43) *EHR data from Salford Integrated Record in UK and case report forms from Salford Lung Study.*	*Algorithms for both **read codes from Rothnie et al., 2016 (38) AND ICD-10 codes from Rothnie et al.,(39)** Results from a 'best-case scenario', using the full algorithm in primary and secondary care, and allowing a maximum gap in the start or end dates of the episodes of up to 15 days*	*Moderate and severe AECOPD episodes reported in the eCRF for a clinical trial*	*3,042*	*73.6%*	-	*69.1%*	-
Echevarria et al., 2020 (46) *2 hospitals in England: one urban and one rural.*	*COPD codes J44*	*Consensus of 2 respiratory specialists using GOLD guidelines*	*1,014*	*63.9%*	*75.5%*	*70.7%*	*69.4%*

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

Awano et al., 2023 (40) *2 acute hospitals in Tokyo*	*COPD codes J410, J411, J42, J43, J44, J449, J841*	*Physician review of patient medical records*	*92*	*72.1%*	*82.9%*	*33.7%*	*96.1%*

Table 8. Detailed summary of Read code validation studies of AECOPD

Study	***Algorithm(s)***	***Gold standard reference***	***N***	***PPV / Derived PPV (95% CI)***	***NPV / Derived NPV (95% CI)***	***Sensitivity / Derived Sensitivity (95% CI)***	***Specificity / Derived Sensitivity (95% CI)***
Rothnie et al., 2016 (38) *UK database (Clinical Practice Research Datalink).* *Age (%):*	*Oral corticosteroid (OCS) prescription*	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*1152*	*73.0% (69.5-76.5)*	-	*30.2% (25.8-34.6)*	-
	Antibiotic prescription	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*5840*	*60.9% (59.0-62.9)*	-	*71.1% (66.8-75.4)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

55-64 = 36.3% *65-74 = 30.5%* *≥75 = 11.7 %*	*Oral corticosteroid and antibiotic prescription (on the same day)*	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*823*	*79.3% (75.8-82.9)*	-	*24.5% (20.4-28.6)*	-
	Exacerbation Symptom definition (increase in 2 or more of: dyspnoea, cough, sputum)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*142*	*64.8% (56.2-73.3)*	-	*2.6% (1.1-4.0)*	-
	Exacerbation Symptom definition and oral corticosteroid prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*88*	*89.8% (82.9-96.7)*	-	*2.2% (0.9-3.6)*	-
	Exacerbation Symptom definition and antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*57*	*93.0% (85.6-100.0)*	-	*1.8% (0.6-3.1)*	-
	Exacerbation Symptom definition and oral corticosteroid & antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from*	*48*	*97.9% (94.5-100.0)*	-	*1.7% (0.5-2.9)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

		patient notes by two respiratory physicians					
	Lower respiratory tract infection (LTRI) code (excluding pneumonia)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*1745*	*79.6% (76.9-82.3)*	-	*23.0% (19.2-26.8)*	-
	LTRI code and oral corticosteroid prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*1558*	*81.4% (78.7-84.1)*	-	*19.9% (16.3-23.5)*	-
	LTRI code and antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*393*	*88.3% (84.4-92.2)*	-	*12.0% (9.3-14.7)*	-
	LTRI code and oral corticosteroid & antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*371*	*88.1% (84.1-92.1)*	-	*11.4% (8.8-14.0)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

	AECOPD code	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*885*	*96.0% (94.5-97.6)*	-	*25.1% (20.9-29.2)*	-
	AECOPD code and oral corticosteroid prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*638*	*96.9% (95.4-98.3)*	-	*18.2% (14.6-21.8)*	-
	AECOPD code and antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*423*	*96.5% (94.5-98.4)*	-	*17.5% (13.8-21.2)*	-
	AECOPD code and oral corticosteroid & antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*377*	*96.8% (95.0-98.6)*	-	*16.0% (12.6-19.5)*	-
***Rothnie et al., 2016 (38)** (subset with*	*Oral corticosteroid (OCS) prescription*	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians*	*367*	*72.2% (66.5-77.9)*	-	*22.7% (16.1-29.2)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

additional patient data)		*(with additional information provided by GPs)*					
	Antibiotic prescription	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*2245*	*61.3% (58.3-64.3)*	-	*63.4% (55.4-71.4)*	-
	Oral corticosteroid and antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*251*	*79.7% (73.5-85.8)*	-	*18.6% (12.4-24.7)*	-
	Exacerbation Symptom definition (increase in 2 or more of: dyspnoea, cough, sputum)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional*	*83*	*63.9% (52.7-75.0)*	-	*2.1% (0.1-4.0)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

		information provided by GPs)					
	Exacerbation Symptom definition and oral corticosteroid prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*50*	*94.0% (88.0-100.0)*	-	*2.1% (0.1-4.0)*	-
	Exacerbation Symptom definition and antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*36*	*94.4% (86.8-100.0)*	-	*1.6% (0.1-3.2)*	-
	Exacerbation Symptom definition and oral corticosteroid & antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional*	*31*	*100% (88.8-100.0)*	-	*1.6% (0.1-3.2)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

		information provided by GPs)					
	Lower respiratory tract infection (LTRI) code (excluding pneumonia)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*693*	*82.8% (78.8-86.9)*	-	*24.7% (18.8-30.7)*	-
	LTRI code and oral corticosteroid prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*621*	*84.5% (80.6-88.5)*	-	*20.6% (15.2-26.0)*	-
	LTRI code and antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional*	*142*	*93.0% (88.3-97.6)*	-	*12.4% (7.8-16.9)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

		information provided by GPs)					
	LTRI code and oral corticosteroid & antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*129*	*92.2% (87.1-97.4)*	-	*10.8% (6.7-15.0)*	-
	AECOPD code	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*350*	*98.3% (96.9-99.6)*	-	*26.8% (19.7-33.9)*	-
	AECOPD code and oral corticosteroid prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional*	*236*	*99.2% (98.1-100.0)*	-	*18.6% (12.4-24.7)*	-

Published online February 5, 2025 https://doi.org/10.15326/jcopdf.2024.0577

		information provided by GPs)					
	AECOPD code and antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*155*	*98.1% (96.0-100.0)*	-	*17.0% (10.8-23.2)*	-
	AECOPD code and oral corticosteroid & antibiotic prescription (on the same day)	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*	*140*	*98.6% (96.8-100.0)*	-	*15.5% (9.7-21.2)*	-
Rothnie et al., 2016 (38) *(subset with additional patient data*	*Algorithms 5, 6, 8, or 12: Symptom definition with prescription of antibiotic or OCS; or LRTI; or AECOPD code*	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional*		*88.1% (85.3-90.8)*	-	*51.6% (44.1-59.0)*	-

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- combined algorithms)		*information provided by GPs)*					
	Algorithms 3, 5, 6, 8, or 12: Prescription of antibiotics and OCS for 5-14 days; or Symptom definition with prescription of antibiotic or OCS; or LRTI code; or AECOPD code	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*		*85.5% (82.7-88.3)*	-	*62.9% (55.4-70.4)*	-
	All algorithms combined	*Review of GP questionnaires and other relevant material from patient notes by two respiratory physicians (with additional information provided by GPs)*		*63.8% (61.0-66.6)*	-	*88.1% (82.9-93.4)*	-
Rothnie et al., 2016	*AECOPD hospitalisation code*	*HES: Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any position or COPD code (J44.9) in*		*50.2% (48.5-51.8)*	-	*4.1% (3.9-4.3)*	-

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(39) (CPRD/Read) *Age (%)* *65-74 = 31.4%* *≥75 = 21.7%* *General UK population using CPRD data and HES.*		*the first position in any FCE during spell*					
	AECOPD identified using validated algorithm and hospitalisation code	*HES: Specific AECOPD code (J44.0 or J44.1) or LRTI code (J22) in any position or COPD code (J44.9) in the first position in any FCE during spell*		*43.3% (42.3-44.2)*	-	*5.4% (5.1-5.7)*	-
	AECOPD hospitalisation code	*HES: Specific AECOPD code (J44.0 or J44.1) in any position or COPD code (J44.9) in the first position in any FCE during spell*		*49.0% (47.3-50.6)*	-	*4.6% (4.5-4.9)*	-
	AECOPD identified using validated algorithm and hospitalisation code	*HES: Specific AECOPD code (J44.0 or J44.1) in any position or COPD code (J44.9) in the first position in any FCE during spell*		*38.5% (37.6-39.4)*	-	*5.5% (5.2-5.9)*	-
	AECOPD hospitalisation code	*HES: Specific AECOPD code (J44.0 or J44.1) in the first position in first FCE during spell*		*45.9% (44.2-47.6)*	-	*4.7% (4.4-4.9)*	-

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	AECOPD identified using validated algorithm and hospitalisation code	*HES: Specific AECOPD code (J44.0 or J44.1) in the first position in first FCE during spell*		*37.2% (36.3-38.1)*	-	*5.7% (5.4-6.0)*	-

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