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REVIEW

Predictors of Acute Exacerbations in COPD: A Systematic Review

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Background: COPD is characterized by acute exacerbations (AECOPD), which drive its progression and burden. AECOPD can be caused by various factors. Better prediction of AECOPD provides opportunity for initiating preventive treatment.

Methods: This systematic review provides an evidence-based overview of clinical predictors of moderate, severe AECOPD and relapse of moderate and severe AECOPD (≤28 days of a previous AECOPD). Cohort studies, case-control studies, or (cluster) randomized controlled trials published in English between January 2011–December 2023 in PubMed, CINAHL, Embase, Web of Science and the Cochrane library were assessed. Eligible studies included patients diagnosed with COPD, aged ≥40 years, and who were current or ex-smokers. Predictors of AECOPD were categorized into: patient characteristics, symptoms, biomarkers, lung function test results, and composite scores. Critical appraisal was performed with the QUIPS-tool.

Results: Out of 1261 screened articles, 30 were included. Sixty-one distinct possible predictors of AECOPD were assessed, of which 37 were statistically significant ($P < 0.05$). Age, AECOPD history, fibrinogen, FEV_1, bronchodilator response, health status measured with the COPD specific St. George's Respiratory Questionnaire (SGRQ-C) score, and COPD GOLD classification (2–4, B-D) were significant predictors of severe and/or moderate AECOPD in more than one article. Only 11 out of the 30 included studies had a low risk of bias.

Discussion: Based on the highest relative statistical significance, combined with the best overall risk of bias, the most promising predictors of AECOPD are history of ≥1 AECOPD, higher SGRQ-C scores, elevated fibrinogen levels, and worse COPD GOLD (2–4, B-D). Future research should focus on standardization of AECOPD and predictor definitions, including the use of clearly defined cut-off values. Given the complexity and heterogeneity of COPD, combining diverse predictor domains into composite measures may enhance predictive accuracy of AECOPD, and the integration of such composites is promising for advancing COPD management in clinical practice.

Keywords: chronic obstructive pulmonary disease, exacerbation, predictors, disease management, prognostic models

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition that is characterized by acute symptom deteriorations, which are known as acute exacerbations of COPD (AECOPD). These AECOPD require a change in regular treatment and/or hospitalization depending on their severity. Mild AECOPD only require treatment with short acting bronchodilators (SABDs); moderate AECOPD with SABDs, oral corticosteroids, and/or antibiotics; and severe AECOPD require a visit to the emergency room or a hospitalization.[1]

AECOPD can be caused by various factors such as respiratory tract infections, environmental factors (eg air pollution), and comorbid conditions (eg heart failure).[2] AECOPD have many detrimental effects on the patient. First, the increased airway inflammation and incomplete resolution of symptoms and physiological function after an AECOPD further accelerates the decline in respiratory function.[3] Second, AECOPD significantly reduce the patients' quality of life and increase functional impairment and mortality.[4] Third, most COPD-related healthcare costs can be attributed to

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AECOPD as these often require extensive treatment during a hospitalization.[4] Furthermore, since one AECOPD increases the risk of another, AECOPD readmission rates are high.[1,5,6] Finally, AECOPD have a negative effect on patients' mood. Patients often suffer from feelings of anxiety, depression and low energy, which negatively impact their personal and social life, resulting in less participation in social activities when experiencing an AECOPD.[3,7,8]

Better predicting AECOPD provides the opportunity to initiate preventive treatment (eg pharmacological therapy).[9] Several patient characteristics (eg sex, body mass index (BMI), age, smoking status, history of AECOPD) have been linked as predictors for AECOPD.[10–12] Moreover, different tools have been assessed on their ability to predict AECOPD, such as the COPD Assessment Test (CAT) or Saint George's Respiratory Questionnaire (SGRQ).[13–15] Although these tools are validated regarding their ability to assess those at risk of AECOPD, they are still not routinely used in clinical practice to predict AECOPD.[5,16]

Symptoms such as dyspnea or cough have also been identified as predictors of AECOPD.[17,18] However, identifying AECOPD based only on patients' symptoms can be difficult due to the variety in these individual symptoms.[16] Furthermore, given the frequent existence of COPD with comorbidities, COPD symptoms lack disease specificity. Therefore, if a patient experiences dyspnea, there may be another underlying cause which should also be assessed such as pneumonia, heart failure, or pulmonary embolism.[1]

Although recent studies reported promising biomarkers to predict AECOPD, eg eosinophils, C-reactive protein (CRP),[19,20] none of these predictors have been implemented yet in standard clinical practice, which so far resulted in the inability to attribute validated biomarkers as a (key) predictor of AECOPD.[20–22] In addition, there is a lack of consistent reporting of objective biomarkers.[23] Consequently, without an increased symptom like dyspnea, these biomarkers cannot specifically be attributed to AECOPD when measured independently.[5,24]

AECOPDs are also linked to a decline in lung function.[25] Lung function test results (eg forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) ratio) are useful in assessing symptomatic COPD.[25] However, there are limitations in their ability of early identifying AECOPD. Although other tests such as walking tests (eg six-minute walk test (6MWT), five-repetition (sit-to-stand test) are seen as powerful predictors in COPD prognosis and show positive results in their ability of predicting AECOPD, they are not routinely used in clinical practice with the purpose of predicting AECOPD.[1,26–29]

Accurately predicting AECOPD and gaining insights into potential evolving COPD exacerbations remains challenging, as there is no validated tool that is currently implemented in routine clinical management of COPD to predict AECOPD.[5,16] Hence, there is a clear need for objectively measurable validated markers to predict AECOPD,[23] that can be implemented in standard clinical practice, to enable timely initiation of preventive treatment. The aim of this systematic literature review was therefore to provide an evidence-based overview of clinical predictors of moderate, severe and relapse of AECOPD, consisting of patient characteristics, symptoms, biomarkers, lung function test results, and composites of these.

Methods

Study Selection

Peer-reviewed studies published in English between January 2011 and December 2023 were examined to identify clinical predictors of moderate AECOPD, severe AECOPD (hospitalizations, including pneumonia) and relapse of moderate and severe AECOPD. The predictors of AECOPD were categorized into one or more of the following five groups:

1. Patient characteristics: defined as individual attributes, health-related factors, and clinical history, including, but not limited to, age, gender, ethnicity, BMI, COPD disease stage (GOLD[30] or ATS/ERS[31]), smoking status, educational level, number of previous AECOPD, number of previous respiratory-related hospitalizations;
2. Symptoms: defined as a physical or mental problem that a person experiences that may indicate a disease or condition[32] (eg dyspnea, cough);
3. Biomarkers: defined as a biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals, or that is a sign of a normal or abnormal process, or of a condition or disease[33,34] (eg eosinophils, fibrinogen, vitamin D);
4. Lung function test results: defined as the results of a respiratory function test (eg FEV_1% predicted, FEV_1/FVC, FVC% predicted); and

5. Composites: defined as a combination of the above mentioned categories (eg BODE index).

The studies included in this review were restricted to cohort studies, case-control studies, or (cluster) randomized controlled trials (RCT). The study participants should have a COPD diagnosis according to the GOLD criteria (post-bronchodilator $FEV_1/FVC < 0.70$)[30] or ATS-ERS criteria,[31] be 40 years of age or older and current or ex-smokers. Additionally, the predictor of AECOPD had to be measured prior to (not during) the AECOPD.

The outcome measures assessed in these studies were moderate and severe AECOPD as well as relapse of AECOPD. Moderate AECOPD was defined as an acute worsening of respiratory symptoms that necessitated additional treatment with antibiotics and/or oral corticosteroids (6). Severe AECOPD was characterized by an acute worsening of symptoms that led to hospitalization.[30] Relapse of AECOPD was defined as the occurrence of a moderate or severe AECOPD within 28 days of a prior AECOPD of either severity.[35] In studies where moderate and severe AECOPD were combined into a single outcome measure, predictors were categorized as "both moderate and severe AECOPD".

A predictor was considered statistically significant if the study reported a statistically significant relation ($p < 0.05$) between the predictor variable and the outcome measure of interest (ie moderate, severe, or relapse of AECOPD). Outcomes presented with only an area under the receiver operating curve (AUROC) were included if the AUROC 95% confidence interval was entirely above 0.5, indicating discriminative performance better than chance.[36] The most promising predictors of AECOPD within their respective category were selected based on the highest relative statistical significance of a predictor and the best overall risk of bias of the studies reporting on the predictor.

Screening Process

This systematic review followed the PRISMA guidelines.[37] A systematic search was conducted in PubMed, CINAHL, Embase, Web of Science and the Cochrane library (see Supplemental information; Appendix A, Table 1A). Snowballing of identified reviews and included articles was performed (CB or DC) to identify additional eligible articles.

First, the references obtained from the search were uploaded in Covidence,[38] a systematic review managing software, and deduplicated. Second, the titles and abstracts of the deduplicated set of articles were screened for eligibility by two independent reviewers (CB or DC and MB or AL or JP or SvD or PV or WB). Third, the full text of the relevant articles was screened for eligibility by two independent reviewers (CB or DC and MB or AL or JP or PV or WB or SvD). Any conflicts during the screening process were resolved by discussion. If no agreement was reached, a third reviewer was consulted to make the final decision.

Data Extraction and Critical Appraisal

Data extraction and critical appraisal (Modified Quality In Prognosis Studies (QUIPS) tool[39]) were performed (CB or DC). The articles were assessed on low, moderate and high risk of bias, for the domains study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting, in line with the assessment of Hayden et al (2013).[39] If no clear judgement could be made based on the information reported in the article, the risk of bias was assessed as unsure. A random sample of the data extraction and critical appraisal was independently assessed or checked by a second reviewer (MB or AL or SvD or JP). Any conflicts were resolved by discussion.

The following data was extracted from the included articles: 1) general information (title, first author, publication year, country), 2) study information (sample size, study design, eligibility criteria, objective), 3) outcome measure (moderate or severe AECOPD, relapse of moderate or severe AECOPD), 4) predictor information (predictor category (patient characteristics, biomarkers, lung function test results, symptoms, composites), predictor variable (eg age, dyspnea, Fibrinogen), cut-off values and performance of the predictor (ie hazard ratio, odds ratio, risk ratio, incidence ratio ratio)), and 5) covariates in the prediction model (eg age, gender, pack-years, 6-minute walking distance (6MWD)).

Results

The search yielded 1261 articles after deduplication. The title and abstract screening resulted in 231 articles for full text screening. Finally, 30 articles reporting on 25 studies were included for data extraction and critical appraisal (Figure 1). Main reasons for exclusion were no measurement of the outcome of interest (n = 55), other study type (n = 29), and other definitions of moderate, severe AECOPD, or relapse of AECOPD (n = 24).

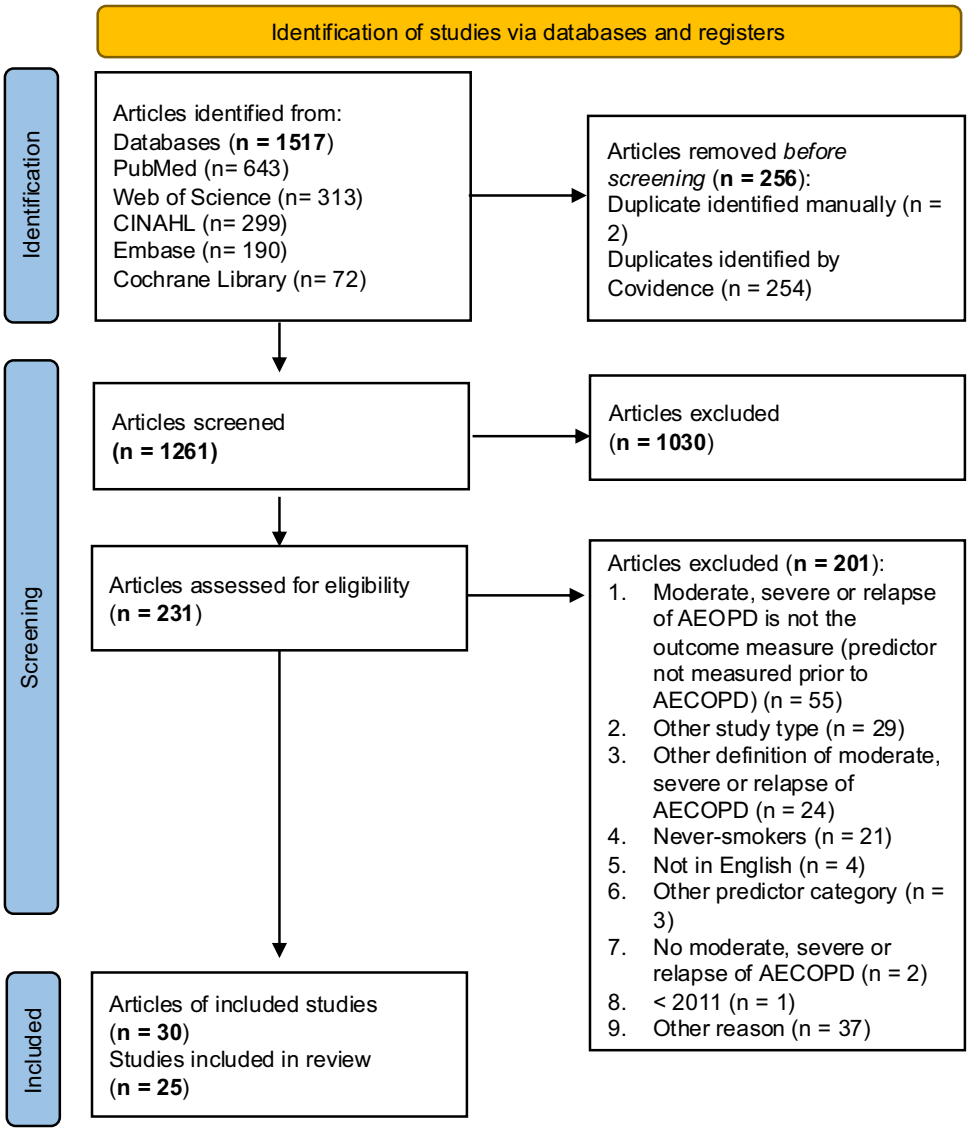

Figure 1 PRISMA 2020 flow diagram[37] for the identification of studies.
Note: Bold font indicates the sum of articles/studies. *No statistical significant relation ($p > 0.05$) reported.
Abbreviations: AreaFE%, area under flow-volume curve; BODE index, composite of body-mass index; airflow obstruction, dyspnea, and exercise capacity, CID, clinically important deterioration; (decrease in FEV_1 of 100 mL, increase of 4 units in St. George's Respiratory Questionnaire, and incidence of moderate and/or severe exacerbation), COPD GOLD-classification (1–4); based on lung function, COPD GOLD-classification A-D; based on symptoms and lung function, FEV1% predicted; Forced expiratory volume in 1 second based on population average, FVC% predicted; Forced vital capacity based on population average, mMRC; modified Medical Research Council Dyspnea scale, $PaCO_2$: Partial pressure of carbon dioxide. SGRQ(-C); St. George's Respiratory Questionnaire (- COPD).

Study Characteristics

Table 1 presents an overview of the 30 included articles (reporting 25 distinct studies) and their characteristics, including 21 cohort studies, three RCTs and one case-control study. The sample size ranged between 15 and 10,000 participants with an age range of 59–75 years old, current smokers varied between 10 and 53%, and a FEV_1% predicted with a range of 39–76%. Studies were conducted in 19 different countries.

Risk of Bias

Of the 30 included articles, only 3 articles[49–51] had a low risk of bias on all six QUIPS domains. Fourteen articles had an overall high risk of bias, five an overall moderate risk and eleven an overall low risk of bias (Table 2).

Table 1 Overview Characteristics and Demographics of Included Articles (n = 30)

Reference	Country	Predictor Field	Period	Study	Study Design (Retro-/ Prospective, Single-/ Multicenter)	Sample Size	Age Mean SD	Sex (Male n, (%))	Smoking Status (Current n, (%))	FEV_1% Predicted
Abe, 2021[40]	Japan	PT CHAR, SYM, LF,	05-2003 until 05-2005		Cohort study (P, M)	259	70 ± 8	244 (94)	73 (28)	65±22
Amado, 2018[41]	Spain	PT CHAR, SYM, BIO, LF, COMP	04-2016 until 02-2017		Case-control study (P, S)	65	67 ± 7	47 (72)	12 (18)	53 ± 17
Andrianopoulos, 2015[42]	Canada, USA, Ukraine, Czechia, Bulgaria, Spain, Slovenia, United Kingdom, Denmark, Norway, Scotland, New-Zealand	PT CHAR, SYM, LF, COMP	2005 −2009	ECLIPSE	Cohort study (P, M)	2010	63 ± 7	1312 (65)	728 (36)	49 ± 16
Brusse-Keizer, 2017[43]	The Netherlands	LF, COMP	12-2005 until 04-2014	COMIC	Cohort study (P, S)	665	67 ± 10	402 (61)	173 (26)	53 ± 19
Burkes, 2020[44]	USA	BIO	12-11-2012 until 31–07-2015	SPIORMICS	Cohort study (P, M)	1609	65 ± 8	936 (58)	529 (33)	61 ± 23
Busch, 2016[17]	USA	PT CHAR, SYM LF, COMP	2007-2012	COPDGene	Cohort study (P, M)	2113	64 ± 8	1737 (48)	680 (32)	49 ± 19
Celli, 2012[45]	USA	LF	01-2003 until 02-2008	UPLIFT	RCT (P, M)	5992	65 ± 9	2251 (75)	1774 (30)	48 ± 13
Chen, 2015[46]	Taiwan	COMP	01-2006 until 12-2012		Cohort study (P, S)	354	76 ± 6.0	330 (93)	251 (71)	63 ± 18
Cushen, 2016[47]	Ireland	SYM	10-2008 until 12–2012		Cohort study (P, S)	65	Median 67 (63–74)	31 (48)	32 (49)	Median 44 (34–56)
Exuzides, 2017[18]	Canada, USA, Ukraine, Czechia, Bulgaria, Spain, Slovenia, United Kingdom, Denmark, Norway, Scotland, New-Zealand	PTCHAR, SYM, BIO, LF	12-2005 until 2010	ECLIPSE	Cohort study (P, M)	2164	63 ± 7	1411 (65)	786 (36)	48 ± 16
Fernandez – Granero, 2015[48]	Spain	LF	No time period reported Follow-up: 6 months		Cohort study (P, S)	15	70 ± 7	N.R.	N.R.	N.R.
Fortis, 2017[49]	USA	LF	01-2008 until 06-2011	COPDGene	Cohort study (P, M)	10000	60 ± 9	5332 (53)	5279 (53)	76 ± 26
Fortis, 2019[50]	USA	LF	01-2008 until 06-2011	COPDGene	Cohort study (P, M)	3340	64 ±9	1968 (59)	1473 (44)	59 ± 23
Fujita, 2021[51]	Japan	LF	09-2011 until 03-2014		Cohort study (P, S)	44	71 ± 8	41 (93)	N.R.	69 ± 24
Garcia-Pachon, 2021[52]	Spain	BIO	No time period reported Follow-up: 14 months		Cohort study (P, S)	106	73 ± 10	83 (78)	N.R.	44 ± 15
Garcia-Rio, 2012[53]	Spain	PT CHAR, SYM, BIO, LF	No time period reported Follow-up: 65 months ± 26 months		Cohort study (P, S)	173	64 ± 8	157 (91)	41 (25)	49 ± 14

(*Continued*)

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Table 1 (Continued).

Reference	Country	Predictor Field	Period	Study	Study Design (Retro-/ Prospective, Single-/ Multicenter)	Sample Size	Age Mean SD	Sex (Male n, (%))	Smoking Status (Current n, (%))	FEV_1% Predicted
Harlander, 2020[54]	Slovenia	PT CHAR, SYM, BIO, LF	Enrolment: 02–2018 until 06–2018, 12month follow-up		Cohort study (P, S)	97	67 ± 8	52 (61)	36 (39)	56 ± 22
Hirai, 2021[55]	Japan	PT CHAR, SYM, BIO, LF	10-2017 until 01-2020		Cohort study (P, S)	234	74 ± 8	234 (100)	N.R.	66 ± 22
Lee, 2019[56]	South Korea	COMP	Start 10–2011, median follow-up time 61 months		Cohort study (P,S)	149	71 ± 8	130 (87)	53 (36)	51 ± 19
Medina – Mirapeix, 2021[29]	Spain	PT CHAR, SYM, LF	01-2015 until 12-2015		Cohort study (P, S)	127	67 ± 8	120 (88)	41 (30)	N.R.
Natori, 2016[57]	Japan	PT CHAR, SYM, LF	09-2011 until 08-2013	*	Cohort study (P, M)	123	67 ± 6	107 (87)	40 (33)	64 ± 22
Naya, 2018[58]	United Kingdom	COMP	No time period reported Follow-up time: 3 years	TORCH	RCT (P, M)	5292	65 ± 8	4046 (76)	2349 (44)	45 ± 13
	Canada, USA, Ukraine, Czechia, Bulgaria, Spain, Slovenia, United Kingdom, Denmark, Norway, Scotland, New-Zealand		12-2005 until 02-2010	ECLIPSE	Cohort study (P, M)	1973	63 ± 7	1284 (65)	705 (36)	49 ± 16
Numata, 2021[59]	Japan	PT CHAR, BIO, LF	01-2018 until 12-2019		Cohort study (R, S)	138	74 (50–92)	120 (87)	20 (14)	67 ± 20
Nuñez, 2020[10]	Spain, Italy, Slovenia, Bulgaria	PT CHAR, SYM, BIO, LF, COMP	Follow-up: 12 months		Cohort study (P, M)	326	67 ± 9	210 (64)	108 (33)	55 ± 20
Sakurai, 2018[60]	Japan	PT CHAR, BIO, LF	04-2010 until 12-2012		Cohort study (P, M)	274	72 ± 8	257 (94)	26 (10)	63 ± 21
Satici, 2021[61]	Turkey	LF, COMP	01-2019 until 07-2018		Cohort Study (R, S)	81	61 ± 9	73 (90)	40 (49)	N.R.
Singh, 2021[62]	United Kingdom	BIO	06-2014 until 07–2017 Follow up: 36 weeks		RCT (P, M)	8094	65 ± 8	5846 (68)	2802 (35)	46 ± 15
Soltani, 2015[63]	Australia	PT CHAR, SYM, BIO, LF	11-2006 until 07-2008		Cohort study (P, S)	150	70 ± 10	74 (49)	60 (40)	39 ± 17
Suetomo, 2014[64]	Japan	PT CHAR, LF, COMP	09-2011 until 08-2013	*	Cohort study (P, M)	123	67 ± 6	107 (87)	40 (33)	64 ± 22
Wilke, 2015[65]	The Netherlands	SYM	12-2005 until 02-2010	Eclipse	Cohort study (P, M)	1832	63 ± 7	53 (62)	659 (36)	49 ± 16

Note: Suetomo 2014[64] and Natori 2016[57] were based on the same study population.

Abbreviations: BIO, Biomarker; COMP, Composite of predictor field; COPDGene, The Genetic Epidemiology of COPD; COMIC, Cohort of Mortality and Inflammation in COPD; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points; K-CCR, Keio COPD Comorbidity Research; IMPACT Informing the Pathway of COPD Treatment; LF, Lung function test result; M, Multicenter; P, Prospective; PT CHAR, Patient characteristic; R, Retrospective; RCT, randomized controlled trial; S, Single center; SPIROMICS, Subpopulations and intermediate Outcomes in COPD Study; SYM, Symptoms; TORCH, Towards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium; USA, United states of America.

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Table 2 Risk of bias for each included article (n=30) according to authors' judgements

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall Risk of Bias
Abe, 2021[40]	✓	?	✓	?	✓	✓	✓
Amado, 2018[41]	●	?	✓	×	✓	✓	×
Andrianopoulos, 2015[42]	✓	✓	●	?	✓	✓	✓
Brusse-Keizer, 2017[43]	✓	●	✓	✓	✓	✓	✓
Burkes, 2020[44]	✓	?	●	×	✓	✓	×
Busch, 2016[17]	✓	?	●	×	✓	✓	×
Celli, 2012[45]	✓	×	●	?	?	?	×
Chen, 2015[46]	✓	●	✓	×	?	?	×
Cushen, 2016[47]	×	×	×	×	?	×	×
Exuzides, 2017[18]	✓	●	✓	✓	?	✓	✓
Fernandez – Granero, 2015[48]	×	✓	✓	?	?	?	×
Fortis, 2017[50]	✓	✓	✓	✓	✓	✓	✓
Fortis, 2019[50]	✓	✓	✓	✓	✓	✓	✓
Fujita, 2021[51]	✓	✓	✓	✓	✓	✓	✓
Garcia-Pachon, 2021[52]	✓	?	✓	✓	×	×	×
Garcia-Rio, 2012[53]	●	?	✓	×	✓	✓	×
Harlander, 2020[54]	●	?	✓	?	✓	✓	●
Hirai, 2021[55]	✓	?	×	?	?	✓	×
Lee, 2019[56]	×	✓	✓	●	✓	✓	●
Medina – Mirapeix, 2021[29]	✓	✓	✓	×	✓	✓	●
Natori, 2016[57]	✓	●	✓	✓	?	●	●
Naya, 2018[58]	✓	✓	✓	?	✓	✓	✓
Numata, 2021[59]	✓	✓	✓	✓	?	?	✓
Nuñez, 2020[10]	✓	✓	✓	?	✓	✓	✓
Sakurai, 2018[60]	✓	×	×	?	✓	✓	×
Satici, 2021[61]	●	**N.A.***	✓	✓	?	✓	●
Singh, 2021[62]	✓	●	✓	✓	●	✓	✓
Soltani, 2015[63]	✓	?	●	✓	×	✓	×
Suetomo, 2014[64]	✓	?	✓	×	×	✓	×
Wilke, 2015[65]	✓	×	✓	?	×	?	×

Note: *N.A.: Not applicable. This risk of bias could not be determined for one article,[61] as this was a retrospective study, based on data from patient files. Risk of bias: low (✓), moderate (●), high (×), and unsure (?), assessed based on the QUIPS tool.[39]

Predictors of AECOPD

Sixty-one possible predictors of AECOPD (patient characteristics n = 12, symptoms n = 8, biomarkers n = 20, lung function test results n = 17, and composites n = 4) were assessed in the 30 included articles. For a full overview of all extracted information per predictor see Supplemental information; Appendix B and table B1.

In total, 37 predictors of AECOPD had a statistically significant correlation ($p < 0.05$) with the outcome measure of interest (Table 3). Of these, 36 reported an effect measure (eg hazard ratio, risk ratio, likelihood) for moderate (n = 16), severe (n = 24), and both moderate and severe AECOPD (n = 17). Figure 2 provides an overview of the number of times statistical significance and non-statistical significance was reported in a prediction model for these 34 predictors. None of the included articles reported predictors of relapse (within 28 days) of AECOPD.

Patient Characteristics

Six patient characteristics were identified as statistically significant predictors: age (7 out of 21 prediction models), BMI (3/10 models), sex (4/12 models), smoking status (1/6 models), history of AECOPD (5/7 models), and daily physical activity (2/2 models).

Older age showed an increased risk of severe AECOPD in four models,[18,29,42,59] and for both moderate and severe AECOPD in two models.[17,59] One article[63] found that younger age was associated with a higher risk of severe AECOPD (readmission within 6 months) with a 3% increase for every year younger in age.

Patients with a low versus normal BMI showed a lower likelihood (−14.5%) of moderate AECOPD within the coming year, and an increased risk (+25.5%) of severe AECOPD in patients with a low versus normal BMI.[18] Patients with a lower BMI were also at a higher risk of both moderate and severe AECOPD compared to patients with a higher BMI.[59]

Females were more likely to experience moderate AECOPD,[18] and both moderate and severe AECOPD.[17] Current smokers had a lower risk of moderate AECOPD compared to former smokers.[18] Patients with a history of at least one or more compared to no history of an AECOPD had a higher probability of moderate AECOPD,[18,40] severe AECOPD,[18,29] or both moderate and severe AECOPD.[10] Additionally, a lower level of daily physical activity resulted in a higher risk of severe AECOPD.[53]

Symptoms

Seven statistically significant predictors were identified in the symptom category: St. George's Respiratory Questionnaire (SGRQ) (4/9 models), St. George's Respiratory Questionnaire-COPD (SGRQ-C) (4/4 models), SGRQ-C domain: dyspnea (2/4 models), SGRQ-C domain: cough and/or sputum (1/2 models), cough (1/6 models) COPD Assessment Test (CAT) (6/11 models), (modified) Medical Research Council (mMRC) dyspnea scale (1/10 models).

Health status (symptoms, activity, and impact on daily life) was measured through the SGRQ, with a higher score indicating lower health status.[66] Two articles[40,42] found a higher SGRQ score to predict severe AECOPD, each using different thresholds. One identified an increased risk at ≥8 points increase over a one year period in the SGRQ total score.[40] Another article found an increased risk for those with a SGRQ score ≥45.[42] A higher compared to a lower SGRQ total score also increased the risk of both moderate and severe AECOPD.[17] Patients with a higher baseline total score in the COPD specific version of the SGRQ (SGRQ-C) were at greater risk of experiencing a moderate AECOPD (+0.6% per SGRQ-C point) within the coming year.[18] The SGRQ-C also predicted severe AECOPD in two articles,[18,65] although with varying thresholds. One article[65] identified a change of 4 points over one year time period to either increase ($\Delta \geq +4$ points) or lower ($\Delta \leq -4$ points) the risk of severe AECOPD, the other article[18] reported +2.2% risk per point increase in SGRQ-C score over a one year time period, compared to patients with a lower score. Additionally, the SGRQ-C also predicted both moderate and severe AECOPD when there is a change of at least four points in the score.[65] SGRQ-C Dyspnea or cough and/or sputum, assessed using the SGRQ-C domain score, predicted moderate AECOPD in patients reporting these symptoms compared to those who did not.[18] Additionally, frequent coughing was statistically significant for both moderate and severe AECOPD among patients using short acting bronchodilators in one article.[17]

Patients with a higher CAT score had an increased risk of severe AECOPD,[55,61,64] moderate AECOPD,[55] and of the combination of moderate and severe AECOPD.[10,64] An mMRC dyspnea scale score of ≥2 was statistically significant in predicting higher risk of severe AECOPD in one article.[41]

Table 3 Overview of the Identified Possible Predictors of AECOPD with Studies That Reported a Statistically Significant Association (P < 0.05) with Moderate, Severe or Both Moderate and Severe AECOPD

A Patient characteristics as possible predictors of AECOPD							
Predictor	**Reference**	**Risk of bias**	**Predictor information**	**Moderate AECOPD**	**Severe AECOPD**	**Both moderate and severe AECOPD**	**AUC/ C-statistic**
Patient characteristic			**Prediction model**	***HR/OR/RR/ IRR/LL/Coef (95%CI)***			***[SN, SP, PPV, NPV; as %] (95% CI)***
Age (years)	Andrianopoulos, 2015[43]	Low	• Cut off value ≥ 65 years 3-year hospitalization		**HR 1.30 (1.11-1.52)**		AUROC 0.54 [SN 0.53, SP 0.55]
	Busch, 2016[17]	High	(Subpopulation: tiotropium)			**OR: 0.93 (0.87-1.00)**	
	Exuzides, 2017[18]	Low	Likelihood (LL) of experiencing an acute exacerbation within the coming year.	LL 0.25%	**LL 2.22%**		
	Medina – Mirapeix, 2021[29]	Moderate	Predicting acute exacerbations in the following year.		**OR: 1.10 (1.02-1.19)**		
	Numata, 2021[59]	Low	Annual acute exacerbation • Higher age		**OR: 1.11 (1.02-1.21)**	**OR: 1.11 (1.02-1.21)**	
	Soltani, 2015[63]	High	The risk of 3- and 6-month cumulative re-attendance rate:		**RR: 0.97 (0.94-0.99)**		
BMI	Exuzides, 2017[18]	Low	Body mass index (BMI): defined as low (20 kg/m2), normal (21 to 30 kg/m2), or high (+30 kg/m2). • Low vs normal Likelihood (LL) of experiencing an acute exacerbation within the coming year.	**LL −14.47%**	**LL 25.55%**		
	Numata, 2021[59]	Low	Low BMI: 21.4 kg/m2, high BMI: 24 kg/m^2 • Low vs high Annual acute exacerbations			**OR: 0.87 (0.77-0.97)**	
Sex	Busch, 2016[17]	High	Female sex (Subpopulation: tiotropium/ICS/LABA)			**OR: 1.53 (1.05-2.21)**	
			Female sex (Subpopulation: SABD)			**OR: 2.56 (1.30-5.03)**	
			Female sex (Subpopulation: ICS/LABA)			**OR: 1.90 (1.19-3.05)**	
	Exuzides, 2017[18]	Low	Female vs male Likelihood (LL) of experiencing an acute exacerbation within the coming year.	**LL 30.53%**	LL 7.92%		
Smoking status	Exuzides, 2017[18]	Low	Current vs former Likelihood (LL) of experiencing an acute exacerbation within the coming year.	**LL −12.71%**	LL 6.85%		

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Table 3 (Continued).

Exacerbation incidence	Abe, 2021[40]	Low	Incidence of moderate or severe acute exacerbation. 4-year risk of e acute exacerbations	**HR: 2.25 (1.28-3.82)**	HR: 0.81(0.23-2.18)		
	Exuzides, 2017[18]	Low	Prior COPD exacerbations, during the 12-month period before baseline; ● ≥1 vs 0. Likelihood (LL) of experiencing an acute exacerbation within the coming year.	**LL 125.81%**	**LL 89.12%**		
	Medina – Mirapeix, 2021[29]	Moderate	Number of moderate or severe acute exacerbations in previous year. ● predicting acute exacerbations in the following year.		**OR: 1.61 (1.17-2.21)**		
	Nuñez, 2020[10]	Low	Number of moderate and severe AECOPD in year prior to inclusion.			**HR (95% CI): 1.94 (1.32-2.84)**	
Daily physical activity (VMUs)	Garcia-Rio, 2012[53]	High	Physical activity was measured over 5 consecutive days using an RT3 triaxial accelerometer (Stayhealthy). Analog-to-digital converted data were recorded every second with accelerometer, then added to produce 1-min movement epochs of vector magnitude units (VMUs). ● For every 10 VMUs increase in daily physical activity		**HR: 0.99 (0.98-0.99)**		
			Association between level of Daily Physical Activity and the number of hospitalizations due to acute COPD exacerbation). ● Q1: <130 VMU ● Q2: 130-200 VMU ● Q3: 200-270 VMU ● Q4 > 270 VMU		Q1: reference Q2: N.S.A. Q3: **IRR: 0.53 (0.29-0.96)**; Q4: **IRR: 0.1 (0.03-0.29)**		
B Symptoms							
Predictor	**Reference**	**Risk of bias**	**Predictor information**	**Moderate AECOPD**	**Severe AECOPD**	**Both moderate and severe**	**AUC/ C-statistic**
Symptom				***HR/OR/RR/ IRR/LL/Coef (95%CI)***			***[SN, SP, PPV,NPV; as %] (95% CI)***
SGRQ	Abe, 2021[40]	Low	Increase ≥ 8 units in SGRQ score from baseline. 4-year risk of acute exacerbations	HR: 1.10 (0.60-1.89)	**HR: 2.59 (1.15-5.53)**		
	Andrianopoulos, 2015[42]	Low	St. George's respiratory questionnaire (SGRQ) ● Cut off value ≥ 45 points 3-year hospitalization		**HR 2.38 (1.99-2.85)**		AUROC 0.66 (SN 0.73, SP 0.50)
	Busch, 2016[17]	High	Total score (Subpopulation: tiotropium/ICS/LABA)			**OR: 1.02 (1.00-1.03)**	
			Total score (Subpopulation: ICS/LABA)			**OR: 1.03 (1.01-1.04)**	

SGRQ-C	Exuzides, 2017[18]	Low	SGRQ total: derived from the SGRQ for COPD (SGRQ-C) questionnaire ● Per unit increase Likelihood (LL) of AECOPD within the coming year.	**LL 0.56%**	**LL 2.19%**		
	Wilke, 2015[65]	High	The COPD specific version of the SGRQ (SGRQ-C) was used. Risk estimates are made for the AECOPD occurring in the two following years. A change of four units in total score is considered as the minimum clinically important difference. 1. groups: 1. clinically significant 1-year deterioration in SGRQ score (Δ ≥ +4 points). 2. non-clinically significant 1-year change in SGRQ score (Δ −3.99 to +3.99 points). 3. clinically significant 1-year improvement in SGRQ score (Δ≤−4 points).		1)Improvement vs no change: HR: 0.94 (0.76-1.17); 2) No change vs deterioration: **HR: 0.77 (0.62-0.97);** 3) Improvement vs Deterioration: **HR: 0.72 (0.58-0.90)**	1)Improvement vs no change: HR: 0.93 (0.82-1.07); 2) No change vs deterioration: **HR: 0.84 (0.73-0.97);** 3) Improvement vs Deterioration: **HR: 0.78 (0.67-0.89)**	
SGRQ-C: Dyspnea symptoms	Exuzides, 2017[18]	Low	Presence of dyspnea was categorized as 0 or 1 according to patient answers to St George's Respiratory Questionnaire for COPD (SGRQ-C) question 3: responses of "most days a week," "several days a week," and "none at all" were tracked separately. ● Most days vs none. Likelihood (LL) of AECOPD within the coming year.	**LL 31.19%**	LL 5.295%		
			Presence of dyspnea was categorized as 0 or 1 according to patient answers to St George's Respiratory Questionnaire for COPD (SGRQ-C) question 3: responses of "most days a week," "several days a week," and "none at all" were tracked separately. ● several days vs none. Likelihood (LL) of AECOPD within the coming year.	LL **29.05%**	LL –0.63%		
SGRQ-C: Cough/ sputum	Exuzides, 2017[18]	Low	SGRQ-Cough and/or sputum were categorized as 0 (less than "most days per week") or 1 ("most days per week"), according to a patient response of "most days a week" to question 1 or 2 (SGRQ-C). Likelihood (LL) of AECOPD within the coming year.	**LL 13.34%**	LL 1.29%		
Cough	Busch, 2016[17]	High	Frequent cough (Subpopulation: SABD)			**OR (95% CI): 2.14 (1.13-4.06)**	
CAT	Hirai, 2021[55]	High	Higher COPD Assessment Test (CAT)-score. Risk factor for annual total acute exacerbations (*b*, standardized regression coefficient):	**B-Coef: 0.16 (0.01-0.32)**	**B-Coef: 0.20 (0.05-0.35)**		
	Nuñez, 2020[10]	Low	COPD Assessment Test (CAT) ● cut-off value: ≥15 Higher CAT score HR:			**HR (95% CI): 1.03 (1.01-1.05)**	AUROC 0.68 (0.62-0.74)
	Suetomo, 2014[64]	High	Total COPD Assessment Test (CAT) score ≥10 points. ● Annual acute exacerbation		**OR: 3.8 (1.1-17.7)**	**OR: 4.5 (1.9-11.3**	Moderate AECOPD: AUROC 0.77; Severe AECOPD: AUROC 0.79
	Satici, 2021[61]	Moderate	COPD Assessment Test (CAT) score. High grade of dyspnea is defined as having a CAT score of ≥10. ● cut-off value: ≥ 20.5		**OR: 1,12 (1.07-1.72)**		AUROC 0.80 (0.64-0.95) [SN 0.72, SP 0.85, PPV 0.42, NPV 0.95]

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Table 3 (Continued).

mMRC	Amado, 2019[41]	High	modified Medical Research Council (mMRC) ● Risk for in the following year	OR: 1.39 (0.79-2.44)	**OR: 2.75 (1.05-7.21)**		
	Cushen, 2016[47]	High	Changes in Modified Research Council (MRC) dyspnea scores between day 1 post-discharge, day 14 and day 42. ● Change at day 14 in MRC score is given in AUROC				**AUROC 0.67 (0.5-0.8)** [SN 0.77, SP 0.55]
C Biomarkers							
Predictor	**Reference**	**Risk of bias**	**Predictor information**	**Moderate AECOPD**	**Severe AECOPD**	**Both moderate and severe AECOPD**	**AUC/ C-statistic**
Biomarker				***HR/OR/RR/ IRR/LL/Coef (95%CI)***			***[SN, SP, PPV,NPV; as %] (95% CI)***
Arterial pH	Soltani, 2015[63]	High	The risk of 3- and 6-month cumulative re-attendance rate increased by 2% for every reduction of 0.01 in pH		**RR: 0.98 (0.96-1.00)**		
$PaCO_2$	Soltani, 2015[63]	High	Partial pressure of carbon dioxide ($PACO_2$), mmHg. The risk of 3- and 6-month cumulative re-attendance rate.		**RR: 1.01 (1.00-1.01)**		
PaO2	Fujita, 2021[51]	Low	In mm Hg Subjects were followed up for 1 year.	**OR 0.88 (0.79-0.99)**			
Fibrinogen	Exuzides, 2017[18]	Low	Continuous, in mg/dL. Likelihood (LL) of AECOPD within the coming year.	**LL 0.080%**	**LL 0.11%**		
	Singh, 2021[62]	Low	Annual rate of COPD acute exacerbations: analyzed post hoc in the fibrinogen population according to a fibrinogen threshold: ≥ 3.5 or <3.5 g/L and by fibrinogen quartiles ● acute exacerbation risk with fibrinogen ≥3.5 g/L: Over a 36-week time period. (Outcome given in rate ratio)	RR: 1.03 (0.95-1.11)	**RR: 1.30 (1.10-1.54)**	**RR: 1.08 (1.00-1.15)**	
Creatinin/ cystatin C	Hirai, 2021[55]	High	● Cut-off value: 0.71 Risk factor for annual total acute exacerbations (*b*, standardized regression coefficient):		**B-Coef: 0.26 (0.10-0.42)**	B-Coef: 0.10 (-0.05-0.25)	
Sarcopenia index	Amado, 2019[41]	High	Sarcopenia index (SI)= ratio serum creatinine/serum cystatin C. ● Lowest SI quartile: < 73.9, Risk for in the following year.	OR: 1.62 (0.54-4.89)	**OR: 5.16 (1.23-21.7)**		
Eosinophils	Harlander, 2020[54]	Moderate	Per percentage (higher). ● Hazard ratio (HR) during 12 months:			**HR: 1.22 (1.05-1.42)**	
NLR	Sakurai, 2018[60]	High	Neutrophil-to-lymphocyte ratio (NLR): the absolute neutrophil count divided by the absolute lymphocyte count. blood samples were drawn at baseline and annually for 3 years, at a time when the disease was stable ● cut off: ≥ 2.7 Risk factor for acute exacerbation over 3 years			**OR: 2.22 (1.10-4.46)**	AUROC 0.63 (0.55-0.72)

Lymphocyte count	Sakurai, 2018[60]	High	Blood samples were drawn at baseline and annually for 3 years, at a time when the disease was stable.			**AUROC 0.60 (0.51-0.68)**	**See column; both moderate/ severe AECOPD*
mean platelet volume (MPV)	Garcia-Pachon, 2021[52]	High	Femtoliters (fL) ● Percentage of readmissions in the first three months after discharge Low: Below or equal to median value. High: Above the median value ● Median value: 9		**low 37%, high 10%** **(p-value 0.001)**		AUROC 0.64
Chitotriosidase	Harlander, 2020[54]	Moderate	Enzymatic activity measured in plasma from venous blood. ● Cut-off value: Per increase of 10 nmol/h/mL. (Subpopulation: ≥1 acute exacerbation in previous year)			**HR: 1.03 (1.01-1.06)**	
D Lung function test results							
Predictor,	**Reference**	**Risk of bias**	**Predictor information**	**Moderate AECOPD**	**Severe AECOPD**	**Both moderate and severe AECOPD**	**AUC/ C-statistic**
Lung function test result				***HR/OR/RR/ IRR/LL/Coef (95%CI)***			***[SN, SP, PPV, NPV; as %] (95% CI)***
FEV_1 % predicted	Andrianopoulos, 2015[42]	Low	Cut off value ≤44% pred. 3-year hospitalization.		**HR 2.40 (2.05-1.82)**		AUROC 0.67 [SN 0.67, SP 0.65]
	Exuzides, 2017[18]	Low	Per 1% increase. Likelihood (LL) of AECOPD within the coming year.	**LL –1.06%**	**LL –2.99%**		
	Harlander, 2020[54]	Moderate	FEV_1 % predicted ● Per percentage (higher) Hazard ratio (HR) during 12-month follow-up period.			**HR: 0.98 (0.96-0.996)**	
	Hirai, 2021[55]	High	FEV_1 % predicted Risk factor for annual total acute exacerbations (*b*, standardized regression coefficient):		B-Coef: -0.05 (-0.21-0.10)	**B-Coef: -0.28** **(-0.43 ; -0.13)**	
	Nuñez, 2020[10]	Low	FEV_1 % predicted ● cut-off value < 55% Lower FEV1(%) HR:			**HR: 0.99 (0.98-0.99)**	AUROC 0.65 (0.59-0.71)
	Sakurai, 2018[60]	High	FEV_1% predicted ● <50%			**OR 2.69 (1.37-5.33)**	AUROC 0.64 (0.57-0.72)
	Soltani, 2015[63]	High	FEV_1 % predicted The risk of 3- and 6-month cumulative re-attendance rate.		**RR: 0.97 (0.95-1.00)**		
FVC% predicted	Soltani, 2015[63]	high	The risk of 3- and 6-month cumulative re-attendance rate.		**RR: 0.98 (0.97-1.00)**		

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Table 3 (Continued).

bronchodilator	Fortis, 2017[49]	Low	Pre bronchodilator FEV_1% predicted: Association of spirometric measures with number of acute exacerbations per year from phase 1 (baseline) to phase 2 visit (5-year interval).	**B-Coef: -0.011 (-0.012-0.01)**	**B-Coef: -0.004 (-0.0045-0.0036)**		
			Post bronchodilator FEV_1% predicted: Association of spirometric measures with number of acute exacerbations per year from phase 1 (baseline) to phase 2 visit (5-year interval).	**B-Coef: -0.011 (-0.01-0.0097)**	**B-Coef: -0.004 (-0.0045-0.0036)**		
			Pre-bronchodilator FEV_1/FVC < 0.7 (PREO): Association of spirometric measures with number of acute exacerbations per year from phase 1 (baseline) to phase 2 visit (5-year interval).	**B-Coef: 0.35 (0.31-0.4)**	**B-Coef: 0.14 (0.11-0.16)**		
			Post-bronchodilator FEV_1/FVC < 0.7 (POSTO): Association with number of acute exacerbations per year from phase 1 (baseline) to phase 2 visit (5-year interval).	**B-Coef: 0.38 (0.34-0.43)**	**B-Coef: 0.14 (0.12-0.16)**		
	Fortis, 2019[50]	Low	increase in pre-bronchodilator FEV_1 and/or FVC ≥12% and ≥200 ml after bronchodilator administration. BDR categories: 1) No-BDR, no BDR by any criteria; 2) FEV_1-BDR, BDR in FEV_1 but no BDR in FVC; 3) FVC-BDR, BDR in FVC but no BDR in FEV_1; 4) Combined-BDR, BDR in both FEV_1 and FVC. All BDR categories had to meet both 12% and 200-ml volume criteria Association of BDR categories at enrolment with drop in FEV1 between baseline and 5-year follow-up visit and respiratory acute exacerbations in subjects with chronic obstructive pulmonary disease. *Models with ATS-BDR binary variable = BDR according to ATS guidelines; Yes or No as the independent variable.	1)reference category; 2) IRR: 1.18 (0.90-1.55); 3)IRR: 1.10 (0.93-1.30); **4) IRR: 1.25 (1.03-1.50);** *ATS-BDR: IRR: **1.16 (1.02-1.32)**	1)reference category; 2): IRR: 0.97 (0.68-1.40); 3) IRR: 1.09 (0.88-1.35); 4) **IRR: 1.34 (1.05-1.71);** *ATS-BDR: IRR: 1.16 (0.98-1.37)		
			Association of bronchodilator response (BDR) categories at enrolment with drop in FEV1 between baseline and 5-year follow-up visit and respiratory acute exacerbations when BDR was defined as a change of FEV1 and/or FVC≥12%.	1)reference category; 2) **IRR: 1.27 (1.04-1.55);** 3) IRR: 1.02 (0.83-1.27); 4): **IRR: 1.26 (1.07-1.48)**	1)reference category; 2) **IRR: 1.33 (1.03-1.72);** 3) IRR: 1.07 (0.81-1.40); 4) **IRR: 1.33 (1.08-1.62)**		
	Celli, 2012[45]	High	Pre-bronchodilator inspiratory capacity (IC) was divided in quartiles, mean (range): 1) Q1, 1.15 (0.45–1.50) 2) Q2, 1.76 (1.51–2.00) 3) Q3, 2.25 (2.01–2.50) 4) Q4, 2.95 (2.51–4.00) Lower quartiles are associated with higher acute exacerbation risk.			1) Q1: HR: **0.81 (0.72-0.92);** 2) Q2: HR: **0.83 (0.73-0.94);** 3) Q3: HR: 0.95 (0.83-1.07); 4) Q4: HR: **0.86 (0.75-0.97)**	
AreaFE% (Airway test)	Satici, 2021[61]	Moderate	*The ratio of area under observed FVL to reference flow volume loop (FVL) was reported as AreaFE%.* ● cut-off value: < 0.17		**OR: 0,84 (0.73-0.97)**		AUROC 0.88 (0.78-0.98) [SN 0.82, SP 0.83, PPV 0.42, NPV 0.96]
Gas trapping% (Airwaytest)	Busch, 2016[17]	High	Subpopulation: tiotropium			**OR: 1.06 (1.02-1.11)**	

Resting breathing instability	Fujita, 2021[51]	Low	Estimated tidal volume (V_T): Breathing instability was assessed by using the coefficient of variation (coefficient of variation percentage = [SD/mean] ×100) for breath-by-breath total duration of respiratory cycle (T) and estimated tidal volume (V) with an arbitrary unit. Subjects were followed up for 1 year.	**OR: 1.13 (1.01-1.27)**			
COPD GOLD classification (1-4)	Brusse-Keizer, 2017[43]	Low	GOLD GOLD 2007 I-IV: Classification into I, II, III or IV by spirometry only A) GOLD I: reference B) GOLD II: reference C) GOLD III: reference		A) **GOLD II: HR: 2.0 (1.1-3.8)** **GOLD III: HR: 4.1 (2.2-7.5)** **GOLD IV: HR: 6.4 (3.2-12.8)** B) **GOLD III: HR: 2.0 (1.5-2.6);** **GOLD IV: HR: 3.1 (2.1-4.7);** C) **GOLD IV: HR: 1.6 (1.1-2.3)**		AUROC 0.69
	Natori, 2016[57]	Moderate	GOLD I-IV: Spirometry was performed in accordance with the American Thoracic Society (ATS)/ European Respiratory Society (ERS) task forces, classification I, II, III, IV. ● GOLD I: reference Annual acute exacerbations.	GOLD II: **RR: 8.06 (1.97-55.0);** GOLD III: **RR: 11.7 (2.15-95.2);** GOLD IV: **RR: 23.3 (1.83-700)**	GOLD II: RR: 3.55x10^6 0.40-infinity); GOLD III: RR: 2.14x10^6 (0.17-infinity); GOLD IV: RR: 2.32x10^6 (0.13-infinity)		
	Suetomo, 2014[64]	High	GOLD I-IV: ● GOLD III and IV Annual acute exacerbation	**OR: 5.7 (2.3-15.3)**	**OR: 3.8 (1.2-12.6)**		
	Numata, 2021[59]	Low	Based on GOLD 2017 guidelines. COPD stage 3/4		OR: 1.2 (0.34-3.9)	**OR: 2.8 (1.1-7)**	
EID *(Exercise test)*	Andrianopoulos, 2015[42]	Low	Exercise-induced oxygen desaturation (EID)= the post exercise oxygen saturation (SpO2) ≤ 88% in the 6-minute walking test. ● ≤ Cut-off value 88 3-year hospitalization		**HR: 1.25 (1.04-1.51)**		
Sit-to-stand test (Exercise test)	Medina – Mirapeix, 2021[29]	Moderate	five-repetition sit-to-stand (5STS): the time (seconds) taken to stand five times from a sitting position, as rapidly as possible. Score 0–4: a higher score indicated greater functional status. - The cut-off score was ≤2 Predicting acute exacerbations in the following year.		**OR: 3.84 (1.14-12.94)**		AUROC 0.79 (0.70-0.88)

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Table 3 (Continued).

6-Minute test (Walking test)	Andrianopoulos, 2015[42]	High	Unintended stops in 6-minute walking test (6MWT): (temporary) discontinuation of the 6MWT. ● Cut-off value: Completers (reference); stoppers 3-year hospitalization		**HR: 1.04 (0.73-1.50)**		
			Six-minute walk-work (6MWW) = 6-minute walk distance * body weight ● cut-off value ≤ 27000 m.kg 3-year hospitalization		**HR: 1.23 (1.01-1.50)**		AUROC 0.62 [SN 0.61, SP 0.56]
	Exuzides, 2017[18]	Low	6-meter walking distance ● In meters Likelihood (LL) of AECOPD within the coming year	**LL 0.04%**	LL 0.03%		
	Medina – Mirapeix, 2021[29]	Moderate	six-minute-walk test (6MWT) The results were categorized into two groups (<350m or ≥350m); <350m was considered poor physical performance. ● Poor 6MWT(<350m): Predicting acute exacerbations in the following year		**OR: 3.20 (1.14-8.96)**		AUROC 0.78 (0.69-0.88)
E Composites							
Predictor	**Reference**	**Risks of bias**	**Predictor information**	**Moderate AECOPD**	**Severe AECOPD**	**Both moderate and severe AECOPD**	**AUC/ C-statistic**
Composite				***HR/OR/RR/ IRR/LL/Coef (95%CI)***			***[SN, SP, PPV, NPV; as %] (95% CI)***
BODE index, (Patient characteristic, symptom, lung function test result)	Andrianopoulos, 2015[42]	High	Calculated using the algorithm developed by Celli and colleagues. ● Cut-off value ≤3 points 3-year hospitalization		**HR: 1.40 (1.08-1.82)**		AUROC 0.69 [SN 0.57, SP 0.69]
	Chen, 2015[46]	High	Participants were classified according to the BODEx index based on BMI, percentage of predicted postbronchodilator FEV_1, mMRC scale, and frequency of severe acute exacerbations, as previously developed. BODEx index scores ranged from 0 to 9 points, and participants were classified into four groups according to their score: Quartile 1 = 0–2 points Quartile 2 = 3–4 points Quartile 3 = 5–6 points Quartile 4 = 7–9 points		1) Q1: reference; 2) Q2: **OR: 6.4 (3.3-12.3)**; 3) Q3: **OR: 8.1 (3.7-17.8);** 4) Q4: **OR: 36.8 (7.8-173.0)**	1) Q1: reference; 2) Q2: OR: **5.9 (3.1-11.3);** 3) Q3: **OR: 5.6 (2.6-12.0);** 4) Q4: **OR: 20.2 (4.4-93.3)**	Severe AECOPD: AUROC 0.73; both moderate and severe AECOPD: AUROC 0.76

CID, (patient characteristic, symptom, lung function test result)	Naya, 2018[58]	Low	Based on patients from the ECLIPSE study. Composite Clinically Important Deterioration (CID) was defined as any one of the following component events: ● Decrease of ≥100 mL from baseline in post-bronchodilator FEV_1. ● Increase of ≥4 units in SGRQ score from baseline. ● Incidence of a moderate/severe acute exacerbation. Patients were categorized into two subgroups: 1. Those who met ≥1 CID criteria within the first 6 months after enrolment (CID+). 2. Those who did not (CID-). ● CID + versus CID-: At 36 months CID+ HR:	**HR: 1.61 (1.50-1.72)**	**HR: 1.55 (1.38-1.73)**		
			Based on patients from the ECLIPSE study. Composite Clinically Important Deterioration (CID) was defined as any one of the following component events: ● Decrease of ≥100 mL from baseline in post-bronchodilator FEV_1. ● Increase of ≥4 units in SGRQ score from baseline. ● Incidence of a moderate/severe acute exacerbation. Patients were categorized into two subgroups: 1. Those who met ≥1 CID criteria within the first 12 months after enrolment (CID+). 2. Those who did not (CID-). ● CID + versus CID-: At 36 months CID+ HR:	**HR: 2.54 (2.20-2.93)**	**HR: 2.81 (2.17-3.63)**		

(*Continued*)

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Table 3 (Continued).

COPD classification (A-D) (symptom, lung function test result)	Brusse-Keizer, 2017[43]	Low	GOLD 2011 ABCD (mMRC): GOLD classification into A, B, C or D via spirometry, history of acute exacerbations and mMRC. 1) GOLD A: reference 2) GOLD B: reference 3) GOLD C: reference		1) GOLD B: N.S.A. HR: NR; **GOLD C: HR: 2.0 (1.3-3.2);** **GOLD D: HR: 4.2 (2.8-6.1);** 2) GOLD C: N.S.A HR: NR; **GOLD D: HR: 2.5 (1.7-3.8)** 3) **GOLD D: HR: 2.1 (1.5-2.8)**		AUROC 0.69
			GOLD 2011 ABCD (CCQ 1.0): GOLD classification into A, B, C or D via spirometry, history of acute exacerbations and CCQ with cut off score 1.0. 1) GOLD A: reference 2) GOLD B: reference 3) GOLD C: reference		1) **GOLD B: HR: 2.7 (1.4-5.1);** GOLD C: N.S.A. HR: NR; **GOLD D: HR: 6.8 (3.7-12.6)** 2) GOLD C: N.S.A. HR: NR; **GOLD D: HR: 2.6 (1.9-3.5)** 3) **GOLD D: HR: 3.7 (2.3-6.2)**		AUROC 0.72
			GOLD 2011 ABCD (CCQ 1.5): GOLD classification into ABC or D via spirometry, history of acute exacerbations and CCQ with cut off score 1.5. 1) GOLD A: reference 2) GOLD B: reference 3) GOLD C: reference		1) **GOLD B: HR: 2.9 (1.7-4.9);** **GOLD C: HR: 2.5 (1.5-4.2)** **GOLD D: HR: 6.3 (4.0-9.9);** 2) GOLD C: N.S.A. HR: NR **GOLD D: HR: 2.1 (1.5-3.2);** **3) GOLD D: HR: 2.5 (1.8-3.4)**		AUROC 0.71
	Chen, 2015[46]	High	GOLD 2013 (ABCD): GOLD 2013 classification into four groups (A–D) based on percentage of predicted postbronchodilator FEV_1, mMRC scale, and risk of recurrent acute exacerbations as defined according to the GOLD 2013 guidelines. A high risk of acute exacerbation was defined as a FEV_1 of less than 50% of predicted, two or more moderate exacerbations, or one or more severe acute exacerbations in the preceding year, according to the GOLD 2013 guidelines. - Gold A: reference		GOLD B: OR: 3.5 (0.9-13.5); GOLD C: **OR: 20.9 (5.2-85.0)** GOLD D: **OR: 31.8 (9.4-107.8)**	GOLD B: OR: 1.7 (0.6-4.3); GOLD C: **OR: 14.1 (4.6-43.2)** GOLD D: **OR: 17.9 (7.6-42.0)**	Severe, and both moderate and severe AECOPD: AUROC 0.79
	Lee, 2019[56]	Moderate	GOLD 2017 ABCD: GOLD classification into A, B, C or D via CAT and mMRC. ● GOLD A: reference		GOLD B: OR: 1.93 (0.67-5.60); GOLD C: **OR: 7.55 (1.25-45.8);** GOLD D: **OR: 25.0 (6.01-102.9)**		AUROC 0.74
			GOLD 2011 ABCD: GOLD classification into A, B, C or D via CAT, mMRC and history of acute exacerbations. ● GOLD A: reference		GOLD B: OR: 1.40 (0.40-4.85); GOLD C: OR: 3.67 (0.79-17.1); GOLD D: **OR: 6.75 (2.07-22.0)**		AUROC 0.71
			GOLD 2007 I-IV: GOLD classification into I, II, III or IV by spirometry only. ● GOLD A: reference		GOLD B: OR: 2.83 (0.31-26.1); GOLD C: OR: 8.24 (0.87-78.2); GOLD D: **OR: 31.5 (2.52-394.4)**		AUROC 0.70

Note: Bold font indicates a statistically significant association ($p < 0.05$).

Abbreviations: HR, Hazard ratio; OR, Odds ratio; IRR, Incidence Rate Ratio; LL, Likelihood; Coef, coefficient; AUC, area under the ROC curve; SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; 95% CI, 95% Confidence Interval; ICS, Inhaled corticosteroids; LABA, long-acting beta-agonists; SABA, short-acting beta-agonists; FEV, Forced expiratory volume; BDR, Bronchodilator; FVC, forced vital capacity; ATS, American Thoracic Society; CAT, COPD Assessment Test; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research council; 6MWT, 6-minute walking test; 6MWD, 6-minute walking distance; 6MWS, 6 minute walking speed; GOLD, Global Initiative for Obstructive Lung Disease; AUROC, values from 0.7–0.8 are considered acceptable; values of 0.5 indicate that there is no discriminative ability to predict AECOPD.[36]

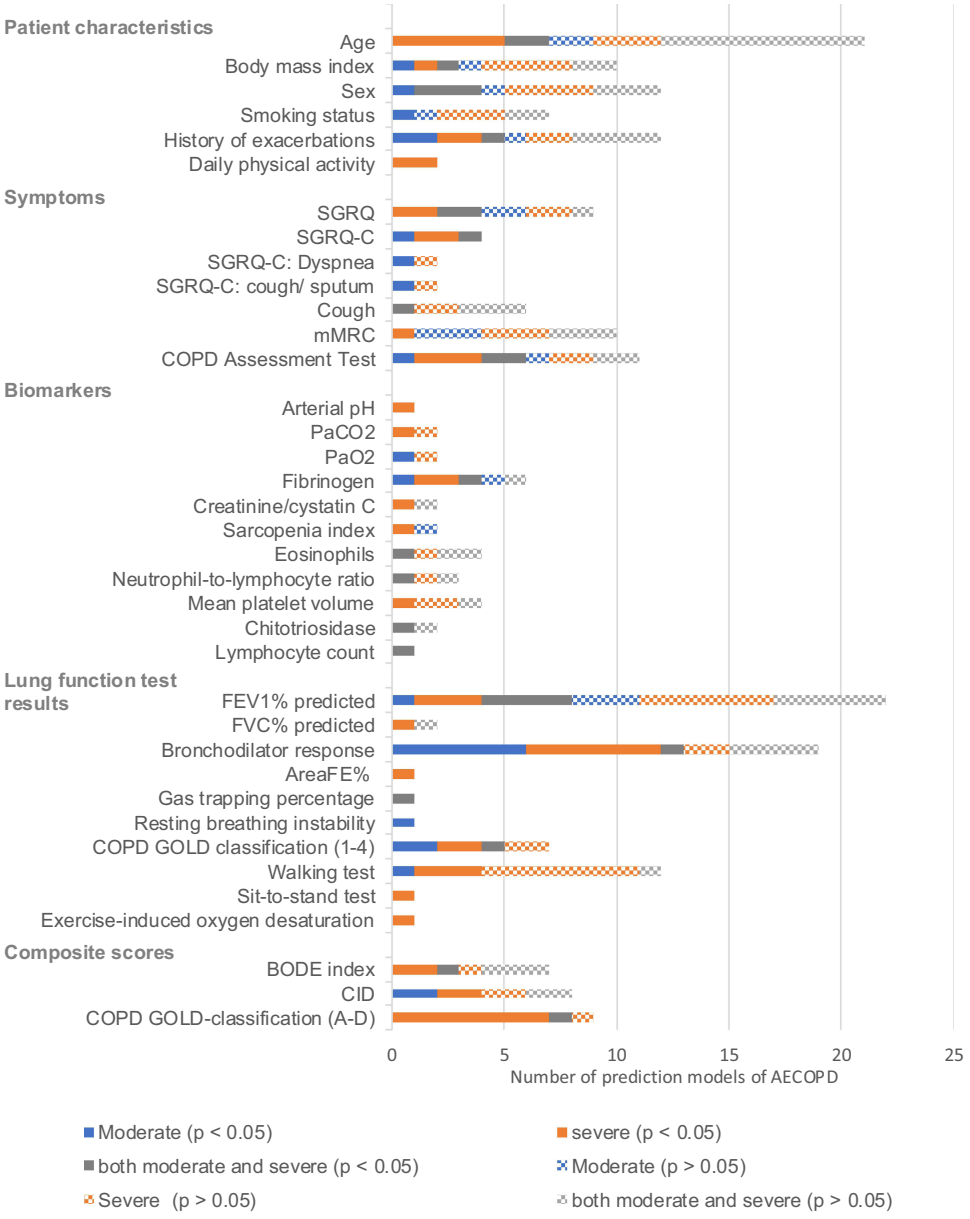

Figure 2 Overview of 37 predictors of moderate, severe, and both moderate and severe AECOPD, with the number of times statistical significance ($p < 0.05$) and non-statistical significance ($p > 0.05$) was reported in a prediction model of AECOPD.

Biomarkers

In the biomarker category, eleven statistically significant predictors for AECOPD were found: arterial pH (1/1 model), $PaCO_2$ (1/2 models), PaO_2 (1/2 models), fibrinogen (4/6 models), creatinine/cystatin C (1/2 model), sarcopenia index (1/2 model), eosinophils (1/4 models), neutrophil to lymphocyte ratio (NLR) (1/3 models), mean platelet volume (MPV) (1/4 model), chitotriosidase (1/2 models), and lymphocyte count (1/1 model).

A lower arterial pH (per 0.01) increased the risk of a new severe AECOPD within 3- and 6-months of a former severe AECOPD.[63] Higher $PaCO_2$ was also identified as a predictor of severe AECOPD in patients with a history of severe AECOPD, with each unit increase raising the risk by approximately 1%.[63] A lower PaO_2 decreased the risk of a moderate AECOPD.[51] Patients with higher baseline fibrinogen levels, in a stable phase, were at a higher risk (+0.1% per mg/dL) of moderate and severe AECOPD.[18] Singh et al (2021) observed that patients with fibrinogen levels of ≥3.5 g/L had a higher risk of severe AECOPD and the combination of both moderate and severe AECOPD.[62] Patients with low serum creatinine/cystatin C levels (<0.71)[55] or a low sarcopenia index (SI) (<73.9)[41] were at higher risk of a severe AECOPD.[55]

Patients with a higher percentage of blood eosinophils,[54] or a baseline NLR above the threshold ≥2.7[60] were at higher risk of both moderate and severe AECOPD. Patients with a lower MPV (≤9fL) had an increased risk of a severe AECOPD.[52] Additionally, higher chitotriosidase activity (per 10 Dnmol/h/mL) in combination with ≥1 AECOPD in the previous year, was a predictor of increased risk of both moderate and severe AECOPD.[54] Finally, based only on an AUROC value with a confidence interval, lymphocyte count is a predictor of AECOPD,[60] with a discriminative ability that is poor (AUROC: 0.60, 95% CI: 0.51–0.68).

Lung Function Test Results

The analysis of lung function test results revealed 10 significant predictors: FEV_1% predicted (8/22 models), FVC % predicted (1/2 models), bronchodilator response (BDR) (13/19 models), airway test: area under flow-volume curve (1/1 models), CT-scan: gas trapping percentage (1/1 models), resting breathing instability (1/1 models), COPD GOLD classification (1–4) (5/7 models), 6-minute walking tests (4/12 models), exercise test: five-repetition sit-to-stand test (1/1 models), and exercise-induced oxygen desaturation (1/1 models).

A 1% lower FEV_1% predicted increased the likelihood of patients experiencing moderate AECOPD by 1.06%.[18] Lower FEV_1% predicted also increased the risk of a severe AECOPD per percentage reduction;[42] specifically, by 3%[18,63] compared to patients with higher FEV_1. A lower FEV_1% was a statistically significant risk for both moderate and severe AECOPD in four articles,[10,54,55,60] two of them specified cut-off values of <55%[10] and <50%,[60] and two increased risk per percentage lower in FEV_1.[54,55] A lower FVC% predicted (per 1%) increased the risk of severe AECOPD by 2%.[63] Combined bronchodilator response[50] and both pre- and post-bronchodilator[49] (defined as an increase in either FEV_1 and/or FVC by 12% and ≥0.2L) were statistically significant in predicting more frequent moderate and severe AECOPD in patients.[49,50] Furthermore, a lower pre-bronchodilator inspiratory capacity was associated with a higher risk of both moderate and severe AECOPD.[45]

Lower area under the flow-volume curve (<0.17) was a predictor for a higher risk of severe AECOPD.[61] Gas trapping on CT scans increased the risk of both moderate and severe AECOPD in one article.[17]

Resting breathing instability was a predictor of moderate AECOPD, where patients with an increased coefficient of variation for tidal volume had a higher risk of moderate AECOPD.[51]

A higher COPD GOLD classification (III or IV versus I–II;[64] II–IV versus I[57]) was associated with a higher risk for moderate[57,64] severe,[64] and both moderate and severe AECOPD.[59] Additionally, a higher COPD GOLD category (II versus I, III versus I–II, IV versus I–III) was found to be a predictor of severe AECOPD in another article.[43]

Patients with a higher compared to those with a lower baseline 6-minute walking distance, predicted a slightly higher risk of moderate AECOPD (+0.04% per meter) within the coming year.[18] In contrast, in two articles[29,42] the risk of severe AECOPD increased for patients with a lower 6-minute walking work (6MWW) (≤27,000 m·kg),[42] unintended stops,[42] and distance <350m[29] during the 6-minute walking test (6MWT), compared to patients a higher 6MWW,[42] no stops,[42] and a 6MWT distance >350 m.[29]

Patients with lower five-repetition sit-to-stand test (≤2),[29] and those with a lower exercise-induced oxygen desaturation (≤88%)[42] had a higher risk of severe AECOPD compared to those with higher five-repetition sit-to-stand test (>2), and exercise-induced oxygen desaturation (>88%).

Composite Predictor Categories

Lastly, in the composite category, the following three statistically significant predictors were identified: BODE index defined as BMI, airflow obstruction, dyspnea and exercise capacity[67] (3/7 models), COPD GOLD classification (A-D, 8/9 models), and composite clinically important deterioration (CID) defined as a decrease in FEV_1 of ≥100 mL, an increase of ≥4 units in the SGRQ and the incidence of a moderate and/or moderate/severe AECOPD[68] (4/8 models).

Patients with a BODE index score of ≥3 had a higher risk of severe AECOPD,[42,46] and for the combination of moderate and severe AECOPD.[46]

Patients with a higher COPD GOLD classification (GOLD B-D) compared to GOLD A were at a higher risk of severe AECOPD.[43,46,56] Also, patients with a COPD GOLD C-D classification compared to GOLD A were at a higher risk for

both moderate and severe AECOPD.[46] Patients who met the composite CID criteria were at a higher risk of moderate, and severe AECOPD.[58]

Discussion

In this review, a total of 37 unique predictors of moderate, severe or both moderate and severe AECOPD were defined in the categories patient characteristics, symptoms, biomarkers, lung function tests, and composites across 30 included articles. None of these articles reported on relapse (within 28 days) of AECOPD. Significant predictors among patient characteristics include age, BMI, sex, smoking status, history of AECOPD and daily physical activity. Higher age and lower BMI are associated with worse COPD outcomes,[69] thus it is unsurprising that these factors predict AECOPD. Notably, one study[18] reported that current smokers had a lower risk of AECOPD compared to former smokers. This finding aligns poorly with existing literature[70,71] and guidelines,[69] but may be explained by reverse causality as smokers with more severe COPD are more likely to quit.[18] A history of AECOPD has been shown to be the best predictor of frequent AECOPD (defined as ≥2 AECOPDs per year),[72] as highlighted in the GOLD 2025 report.[69] The current review identified in studies with a low risk of bias that patients with a history of at least one AECOPD already had a significantly increased risk of AECOPD.[10,18] These findings validate the GOLD approach of using exacerbation history as a predictor of AECOPD. However, the threshold of ≥2 AECOPDs per year may be overly restrictive, potentially delaying timely preventative interventions. It is not surprising that lower daily physical activity showed to be associated with a higher risk of AECOPD[53] in this review, since exercise is recommended for COPD management and lowers the risk of acute exacerbations.[69] Contrary to COPD GOLD guidelines, one study in this review found that patients with a younger age had an increased risk of a new severe AECOPD within three and six months.[63] According to the authors of this study, this was due to the greater COPD disease severity observed in younger individuals within this study.[63]

Within the category of symptoms, SGRQ score, SGRQ-C score, SGRQ-C domains score: cough and/or sputum, and dyspnea, mMRC scores, cough, and CAT score were all predictors of AECOPD. SGRQ-C score showed to be the most promising predictor, based on the highest relative statistical significance in its ability to predict AECOPD and the best overall risk of bias. Notably, based on the articles in this review, the potential of the SGRQ-C to predict AECOPD extends beyond its total score to its individual domain scores of dyspnea and cough.[17,18] In contrast, the mMRC and CAT score demonstrated weaker predictive performance of AECOPD, with a higher frequency of non-significant models. These findings suggest that they have limited utility as predictive tools. Additionally, the statistical significance reported for the mMRC is derived from studies with a high risk of bias, whereas the studies reporting on the CAT have varying levels of bias. Consequently, the routine use of mMRC and CAT as predictor of AECOPD should be reconsidered. The original SGRQ is not routinely used in clinical practice mostly due to its length and complexity.[16] Both SGRQ and SGRQ-C are predictive, though standard assessment through the shorter version (SGRQ-C) could provide a more user friendly and reliable alternative.

Several biomarkers predicted an increased risk of AECOPD, including higher fibrinogen levels, higher blood eosinophils percentage, higher chitotriosidase levels, lower sarcopenia index, lower creatinine/cystatin C levels, and low mean platelet volume. Higher fibrinogen levels seem the most promising biomarker based on the high relative frequency of statistical significant models and the accompanied low risk of bias.[18,62] Higher fibrinogen set at a cut-off value of ≥3.5g/L has been proposed to identify patients at elevated risk.[62] These findings are in line with previous reviews as they have already shown similar promising predictive ability with a threshold of 3.5g/L.[22,73] The assessment of fibrinogen in clinical practice could therefore be a next logical step for predicting patients at risk of AECOPD. Whereas blood eosinophils have been assessed in multiple studies,[52,54,60] only one found statistical significance in its predictive ability of AECOPD.[54] The GOLD 2025 report suggests a threshold of ≥300 μL for identifying patients at risk of AECOPD and who are more likely to benefit from preventative treatment with inhaled corticosteroids.[69] However, there is inconsistency across studies on whether blood eosinophils are able to predict acute exacerbations[74,75] and which threshold is appropriate.[23] Hence, there is insufficient evidence to recommend eosinophils as individual predictors of AECOPD. Since all biomarkers, except for fibrinogen, were statistically significant in only one study with either moderate or high risk of bias, additional research is needed. Future studies should establish clear thresholds and validate the predictive ability of biomarkers before these can be further implemented in clinical practice.

In the category of lung function test results, higher COPD GOLD classification (1–4), lower FEV_1% predicted, lower FVC% predicted, lower bronchodilator response, lower area under the flow-volume curve, gas trapping, resting breathing

instability, lower 6-minute walking test results, and lower exercise-induced oxygen desaturation are all statistically significant predictors of AECOPD. All the included articles that reported on the COPD GOLD classification (1–4), although with varying risks of bias, found statistical significance in its ability to predict AECOPD. This is not an unexpected finding, since the former COPD GOLD classification (1–4) is based on the FEV_1,[69] and the predictor $FEV_{1\%}$ predicted also showed to be an independent predictor of AECOPD, albeit in studies with varying risk of bias. A noteworthy finding was that one study with a low risk of bias[18] identified a higher six-minute walk distance as a risk predictor for moderate AECOPD, which might be due to possible confounding factors. All other studies, with worse overall risk of bias, showed that a poorer six-minute walk or exercise test performance was associated with increased AECOPD risk. Exercise tests such as the 6-minute walking tests, exercise-induced oxygen desaturation, and the five-repetition sit-to-stand test showed that patients with a better test result had a better outcome (ie lower AECOPD incidence) than those with worse test results. Since impaired physical function has been associated with worse prognosis in COPD,[76] it is not surprising that worse results on exercise related tests are predictive for a higher risk of AECOPD.

Of the composite predictors, elevated BODE index scores, COPD GOLD classification (A-D) as a composite measure, and Clinically Important Deterioration were all statistically significant predictors of AECOPD. As expected, the COPD GOLD classification (A-D)—which includes both lung function tests and symptom-based questionnaires (eg CAT, mMRC, clinical COPD questionnaire)—was better at predicting a severe AECOPD, and combined moderate and severe AECOPD, than the COPD GOLD classification based on solely lung function. Since the components of COPD GOLD 1–4 classification (FEV_1, mMRC, and CAT) were all independently predictors of AECOPD, it is reasonable to expect that combining these predictors would improve its predictive ability. Due to the complexity and heterogeneity of COPD phenotypes, combining multiple categories of predictors (into composites) may significantly enhance the accuracy of AECOPD risk prediction. COPD is increasingly recognized as a systemic disease, with extrapulmonary manifestations such as cardiovascular comorbidities, metabolic dysfunction, skeletal muscle wasting, and systemic inflammation contributing to its clinical course and prognosis. These systemic features vary across phenotypes and influence both the frequency and severity of acute exacerbations.[69] In this context, integrating the most promising predictors of AECOPD from the five categories (history of acute exacerbations, SGRQ-C score, fibrinogen levels, COPD GOLD 2–4, and COPD GOLD B-D classification) may enhance both short- and long-term risk prediction. Accurately predicting AECOPD is crucial for effective disease management. This involves two key types of predictors: long-term predictors that indicate a patient's general susceptibility to AECOPD, and short-term predictors that signal a likely AECOPD in the near future. Long-term predictors like history of acute exacerbation identify patients at risk of AECOPD and provide valuable insight into those who require close monitoring and optimized clinical management (eg change in pharmacological therapy, a self-management program or pulmonary rehabilitation program). Timely identifying short-term predictors of AECOPD, such as biomarkers (elevated fibrinogen levels) or symptoms (increased cough), is relevant for early deterioration intervention. By recognizing and monitoring both short- and long-term predictors of AECOPD management and prevention of AECOPD improves, hospitalizations reduce, and ultimately healthcare utilization and societal burden reduce.[77] Telemonitoring, a rapidly evolving technology, is a promising tool for identifying more short-term predictors. It allows for personalized tracking of symptoms and physiological changes in real-time such as home-based lung function tests and biomarkers.[78,79]

A key strength of this systematic review is the assessment of a broad range of predictor categories. Evaluating multiple possible predictors or risk factors provides a clearer picture of what might be causing an AECOPD. This review confirmed known predictors and systematically reported the relative frequency of statistical significance of each predictor and the risk of bias in the studies from which these predictors were derived. Additionally, identifying predictors for moderate, severe AECOPD, and relapse of AECOPD ensures that the main types of AECOPD, which result in the highest loss in quality of life and healthcare costs,[4] are considered.

However, the review is not without limitations. Although we aimed to provide an overview of the predictors of AECOPD, it does not encompass all potential predictors. Only predictors categorized as biomarkers, symptoms, lung function test results, patient characteristics or composite scores were considered. Beyond these categories, additional predictors such as meteorological factors have been studied, but their impact on COPD is not fully clear.[69,80–82] Additionally, articles or analyses that included data from never-smokers were excluded, as smoking-related COPD is

the most prevalent form of the disease. Combining predictors from smoking-related and non-smoking-related COPD might not be ideal because the underlying mechanisms and risk factors can differ significantly. There were inconsistencies in the definitions for moderate and severe acute exacerbations, as well as the timeframes for relapse of AECOPD, leading to the exclusion of certain articles or outcomes in this review. These differences in definitions may impact comparability of results across studies, and using the standardized definitions should be considered in future research.

Since only about a third of the included studies in this review had a low risk of bias, future studies should aim to minimize and transparently account for bias. Clearly defining and reporting the study design, will improve methodological quality, hence, prevent concerns about bias.[83] Additionally, integrating composites of the analyzed categories, rather than relying on single predictors, may enhance predictive accuracy and improve risk prediction assessment for AECOPD. Notably, among all included articles, only a few predictors demonstrated statistical significance in more than one study. Therefore, further validation research is necessary to confirm these single-study predictors, prior to their integration into clinical practice.

Conclusion

The most promising predictors of AECOPD within the five categories are history of acute exacerbations, SGRQ-C score, fibrinogen levels, COPD GOLD 2–4, and COPD GOLD B-D classification, based on the highest relative statistical significance combined with low overall risk of bias. By combining multiple predictors into composites, the risk prediction of AECOPD may be enhanced. Future research should focus on these composite risk scores and explore the roles of both long- and short-term predictors in guiding COPD management. However, methodological inconsistencies underscore the need for standardized definitions of moderate, severe or relapse of AECOPD and further validation of predictors in studies with a low risk of bias.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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