

The Acute COPD Exacerbation Prediction Tool (ACCEPT): a modelling study

Amin Adibi, Don D Sin, Abdollah Safari, Kate M Johnson, Shawn D Aaron, J Mark FitzGerald, Mohsen Sadatsafavi



Summary

Background Accurate prediction of exacerbation risk enables personalised care for patients with chronic obstructive pulmonary disease (COPD). We developed and validated a generalisable model to predict individualised rate and severity of COPD exacerbations.

Methods In this risk modelling study, we pooled data from three COPD trials on patients with a history of exacerbations. We developed a mixed-effect model to predict exacerbations over 1 year. Severe exacerbations were those requiring inpatient care. Predictors were history of exacerbations, age, sex, body-mass index, smoking status, domiciliary oxygen therapy, lung function, symptom burden, and current medication use. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE), a multicentre cohort study, was used for external validation.

Results The development dataset included 2380 patients, 1373 (58%) of whom were men. Mean age was 64.7 years (SD 8.8). Mean exacerbation rate was 1.42 events per year and 0.29 events per year were severe. When validated against all patients with COPD in ECLIPSE (mean exacerbation rate was 1.20 events per year, 0.27 events per year were severe), the area-under-curve (AUC) was 0.81 (95% CI 0.79–0.83) for at least two exacerbations and 0.77 (95% CI 0.74–0.80) for at least one severe exacerbation. Predicted exacerbation and observed exacerbation rates were similar (1.31 events per year for all exacerbations and 0.25 events per year for severe exacerbations vs 1.20 events per year and 0.27 events per year). In ECLIPSE, in patients with previous exacerbation history (mean exacerbation rate was 1.82 events per year, 0.40 events per year were severe), AUC was 0.73 (95% CI 0.70–0.76) for two or more exacerbations and 0.74 (95% CI 0.70–0.78) for at least one severe exacerbation. Calibration was accurate for severe exacerbations (predicted 0.37 events per year vs observed 0.40 events per year) and all exacerbations (predicted 1.80 events per year vs observed 1.82 events per year).

Interpretation This model can be used as a decision tool to personalise COPD treatment and prevent exacerbations.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by symptoms of breathlessness and cough, which worsen acutely during exacerbations.¹ COPD is known to be a heterogeneous disorder with large variations in risk of exacerbation across patients.² In clinical practice, a history of two or more exacerbations and one severe exacerbation per year is used to guide therapeutic choices for exacerbation prevention.³ However, this approach is clinically restricted owing to substantial heterogeneity in risk even within those who frequently exacerbate.⁴

Prognostic clinical prediction tools enable personalised approaches to disease management. Despite potential benefits, no such tool is routinely used in clinical management of COPD. Whereas, for COPD-related mortality, clinical scoring schemes, such as the BODE index, are available and frequently used.⁵ A 2017 systematic review by Guerra and colleagues⁶ identified 27 prediction tools for COPD exacerbations. Among these tools, only two reported on model validation and

none were deemed ready for personalised COPD management in clinic.⁶

In this study, we describe a new model, the Acute COPD Exacerbation Prediction Tool (ACCEPT), to predict, at an individual level, rate and severity of COPD exacerbation, report on its performance in an independent external cohort, and explain, using case studies, its potential clinical application. As a decision tool, ACCEPT provides a personalised risk profile that allows clinicians to tailor treatment regimens to individual needs of patients.

Methods

Participants and study design

In reporting our prediction model, we followed recommendations set by the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement.⁷ We developed the model using data from patients with COPD, without previous or existing history of asthma, and who had at least one exacerbation over the past 12 months. We then

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Respiratory Evaluation Sciences Program, Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences (A Adibi MSc, Dr A Safari PhD, K M Johnson MSc, M Sadatsafavi PhD), Division of Respiratory Medicine, Department of Medicine, The UBC Centre for Heart Lung Innovation, St. Paul's Hospital (Prof D D Sin MD), Institute for Heart and Lung Health, Division of Respiratory Medicine, Faculty of Medicine (Prof J M FitzGerald MD, Dr M Sadatsafavi), and Centre for Clinical Epidemiology and Evaluation (Dr M Sadatsafavi), University of British Columbia, Vancouver, BC, Canada; and Ottawa Hospital Research Institute, University of Ottawa, Ontario, Canada (Prof S D Aaron MD)

Correspondence to: Prof Don D Sin, Division of Respiratory Medicine, Department of Medicine, The UBC Centre for Heart Lung Innovation, St. Paul's Hospital, University of British Columbia, Vancouver, BC V6Z 1Y6, Canada don.sin@hli.ubc.ca

Research in context

Evidence before this study

Preventing future exacerbations is a major goal in COPD care. Because of adverse effects, preventative treatments should be reserved for those at a high risk of future exacerbations. Predicting exacerbation risk in patients can guide these clinical decisions. A 2017 systematic review reported that of 27 identified COPD exacerbation prediction tools, only two had reported external validation and none were ready for clinical implementation. To find studies that were published afterwards, we searched PubMed for articles on development and validation of COPD exacerbation prediction from Jan 1, 2015, to May 1, 2019, using search terms “COPD”, “exacerbation”, “model”, and “validation” and no language restrictions. We included studies that reported prediction of risk or rate of exacerbations and excluded studies that did not report external validation. Our literature search revealed two more prediction models, neither of which was deemed generalisable because of absence of methodological rigour, or local and insufficient data available to investigators.

Added value of this study

We used data from three randomised trials to develop ACCEPT, a clinical prediction tool based on routinely available predictors

for COPD exacerbations. We externally validated ACCEPT in a large, multinational prospective cohort. To our knowledge, ACCEPT is the first COPD exacerbation prediction tool that jointly estimates the individualised rate and severity of exacerbations. Successful external validation of ACCEPT showed that its generalisability can be expanded across geographical areas and beyond the setting of therapeutic trials. ACCEPT is designed to be easily applicable in clinical practice and is readily accessible as a web application.

Implications of all the available evidence

Guidelines rely on exacerbation history as the sole predictor of future exacerbations. Simple clinical and demographic variables, in aggregate, can be used to predict COPD exacerbations with improved accuracy. ACCEPT enables a personalised approach to treatment based on routinely collected clinical data by allowing clinicians to objectively differentiate risk profiles of patients with a similar exacerbation history. Care providers and patients can use individualised estimates of exacerbation risk to decide on preventive therapies on the basis of objectively established or patient-specific thresholds for treatment benefit and harm. COPD clinical researchers can use this tool to target enriched populations for enrolment in clinical trials.

externally validated the model in patients with COPD regardless of their exacerbation history and in a subset of patients with COPD with at least one exacerbation over the past 12 months.

For discovery, we pooled data across all groups of three randomised controlled trials: Macrolide Azithromycin to Prevent Rapid Worsening of Symptoms Associated With COPD (MACRO),⁸ Simvastatin in the Prevention of COPD Exacerbations (STATCOPE),⁹ and the Optimal Therapy of COPD to Prevent Exacerbations and Improve Quality of Life (OPTIMAL).¹⁰ In a secondary analysis, we only used placebo groups of trials. We used an independent longitudinal COPD cohort study, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE),¹¹ for external validation. Details of these studies have been previously published. Briefly, the MACRO study⁸ assessed the effect of daily low-dose azithromycin therapy on rate of exacerbations in patients with COPD; the STATCOPE study assessed effects of daily simvastatin therapy on rate of exacerbation,⁹ and the OPTIMAL study assessed effects of tiotropium, fluticasone, plus salmeterol on rate of exacerbation compared with tiotropium plus fluticasone, and tiotropium alone.¹⁰ In all three trials, which comprised the development dataset, patients who had history of at least one exacerbation over the past 12 months were recruited. By contrast, ECLIPSE was a multicentre, 3-year, non-interventional observational study with the primary aim to characterise COPD phenotypes and

identify novel markers of disease progression.¹¹ This study included patients irrespective of their previous history of an exacerbation (table 1). The model is available to use as an interactive web application.

Outcomes

Outcomes of interest were rates of exacerbations and severe exacerbations over 1 year. Exacerbations were the primary outcome of all three trials and a major outcome measure of the ECLIPSE study. All studies used a similar definition of exacerbations, which was formed on the basis of criteria endorsed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) scientific committee.³ Exacerbation was defined as an acute episode of intensified symptoms that required additional therapy.³ Mild exacerbations were defined as those treated with short-acting bronchodilators. Moderate exacerbations were those that required administration of systemic corticosteroids or antibiotics, or both, and severe exacerbations were those that required an emergency department visit or admission to hospital.^{3,8–10}

Predictors

To minimise risk of bias, optimism, and overfitting, no data-driven selection of variables was done. We prespecified predictors on the basis of clinical relevance and availability of predictors in all datasets. Predictors included the number of non-severe as well as severe exacerbations over the previous year, baseline age, sex,

For the ACCEPT web application
see <http://resp.core.ubc.ca/ipress/accept>

	Design	Intervention	Study period (follow-up)	Centres	Inclusion criteria	Exclusion criteria
Development						
MACRO	Randomised trial	Azithromycin	From March 2006 to June 2010 (1 year)	17 sites in USA	Older than 40 years, clinical diagnosis of COPD, at least 10 pack-years of smoking, oxygen or systemic glucocorticoids therapy in the past year, emergency visit or admission to hospital	Asthma, exacerbation in the past month, heart rate above 100 beats per min, QT _c more than 450 ms, QT _c prolonging or torsades de pointes-related medication except for amiodarone, hearing impairment
STATCOPE	Randomised trial	Simvastatin	From March 2010 to January 2014 (about 2 years)	45 sites (29 in USA and 16 in Canada)	Aged 40–80 years, clinical diagnosis of COPD, at least 10 pack-years of smoking, receiving supplemental oxygen or treatment with glucocorticoids or antibiotics, or emergency visit or admission to hospital in the past year	Asthma; receiving statins or indication for statins; on drugs that contradicted with statins; unable to take statins; active liver disease, alcoholism, or allergy
OPTIMAL	Randomised trial	Tiotropium with salmeterol or fluticasone-salmeterol	From October 2003 to January 2006 (1 year)	27 sites in Canada	Older than 35 years, clinical diagnosis of COPD, at least 10 pack-years of smoking, exacerbation requiring systemic glucocorticoids or antibiotics therapy in the past year	Asthma before aged 40 years; congestive heart failure with persistent severe left ventricular dysfunction; oral prednisone; intolerance to tiotropium, salmeterol, or fluticasone-salmeterol; glaucoma; urinary tract obstruction; lung transplant or volume reduction; diffuse bilateral bronchiectasis; pregnancy or breastfeeding
Validation						
ECLIPSE	Cohort	..	From December 2005 to February 2010 (3 years)	46 sites in 12 countries	Aged 40–75 years, clinical diagnosis of COPD, more than 10 pack-years of smoking	Respiratory disorders other than COPD, reported exacerbation in the past month, clinically significant inflammatory disease

COPD=chronic obstructive pulmonary disease. ECLIPSE=Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points. MACRO=Macrolide Azithromycin to Prevent Rapid Worsening of Symptoms Associated With COPD. OPTIMAL=Optimal Therapy of COPD to Prevent Exacerbations and Improve Quality of Life. QT_c=corrected QT interval. STATCOPE=Simvastatin in the Prevention of COPD Exacerbations.

Table 1: Available datasets with data on rate, time, and severity of COPD exacerbations

smoking status, post-bronchodilator FEV₁ (% of predicted),¹² St George's Respiratory Questionnaire score, body-mass index, and use of COPD and non-COPD medications, as well as domiciliary oxygen therapy during the previous 12 months. COPD medications were defined as long-acting muscarinic receptor antagonists, long-acting β_2 agonists, and inhaled corticosteroids. In addition to baseline medications, the model adjusted for treatment assignment in the therapeutic trials (azithromycin in MACRO; statins in STATCOPE; long-acting muscarinic receptor antagonists, long-acting β_2 agonists, and inhaled corticosteroids in OPTIMAL). To facilitate clinical implementation, a web application was created (on the basis of conversion factors that have been previously published), which enables use of a COPD Assessment Test score in lieu of St George's Respiratory Questionnaire.¹³

Follow-up

We applied administrative censoring at 1-year follow-up for patients who had data beyond this threshold. The decision to limit predictions to 1 year was made a priori on the basis of the assumption that predicting exacerbations beyond this time frame was considered less relevant for clinical management of COPD and that prediction accuracy of the model would decrease substantially.

Statistical analysis

We used a joint accelerated failure time and logistic model to characterise rate and severity of exacerbations. We have previously published details of this approach elsewhere.¹⁴ In summary, this framework assigns two random-effect

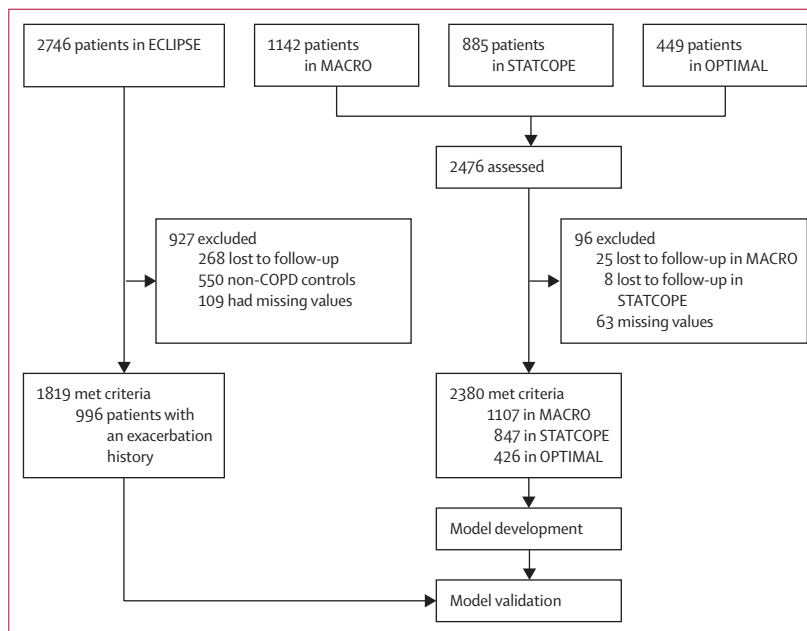


Figure 1: Flow diagram

terms to each individual, quantifying their specific rate of exacerbation and the probability that once exacerbation occurs, it will be severe (appendix p 3). For each patient, this framework fully specifies the hazard of all exacerbations (including their severity) at any given timepoint during follow-up, enabling different predictions, such as the probability of having a specific number of total and severe exacerbations during the next 12 months.

See Online for appendix

For statistical code and
additional resources see
[http://resp.core.ubc.ca/research/
Specific_Projects/accept](http://resp.core.ubc.ca/research/Specific_Projects/accept)

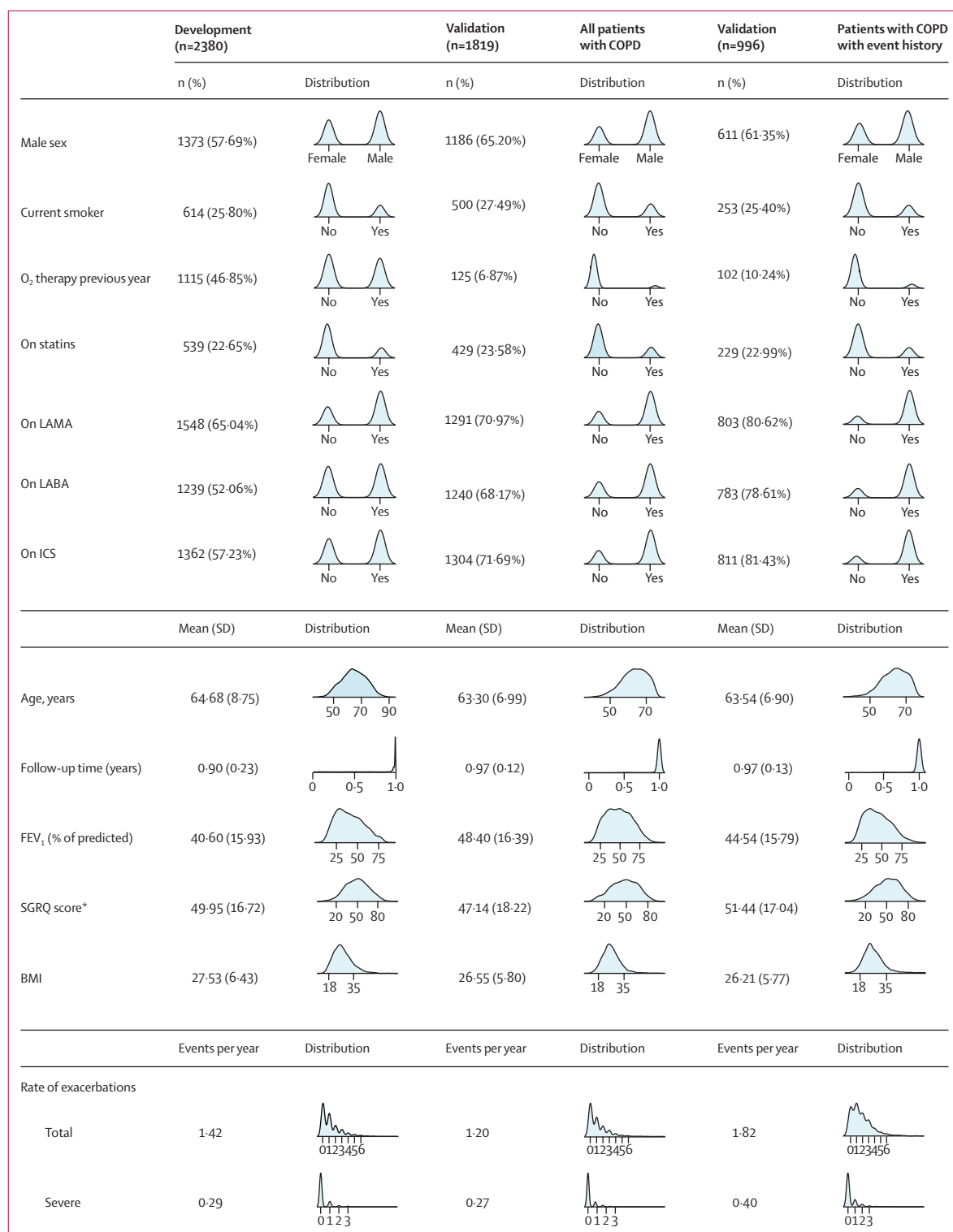


Figure 2: Baseline characteristics in final development and validation datasets

BMI=body mass index. COPD=chronic obstructive pulmonary disease. FEV₁=forced expiratory volume in 1 s. ICS=inhaled corticosteroids. LABA=long-acting β agonist. LAMA=long-acting muscarinic receptor antagonist. SGRQ=St George's Respiratory Questionnaire. SD=standard deviation. *Between 0 and 100, with a higher score indicating worse status.

Two forms of uncertainty in predictions were quantified: uncertainty due to the finite sample of the validation set (represented by 95% CI around the mean of projected values) and uncertainty due to differences in patients' specific exacerbation frequency and severity (represented by the 95% prediction interval around the mean, the interval which has a 95% probability to contain a future observation of a patient with the same predictors). Shrinkage methods were not applied because of low risk of bias due to complete prespecification of the model and high number of events per predictor in the development dataset.¹⁵

Because in this framework, correlation between previous and future exacerbation rates is modelled through random-effect terms, history of exacerbations did not enter the model as a predictor. Instead, a Bayesian approach was used to model distribution of future exacerbation rate and severity, given the exacerbation history of an individual (appendix p 4). Availability of full exacerbation history in the external validation cohort enabled validation of this approach. We did statistical analyses using SAS, version 9.4, and R, version 3.6.1.

External validation

We used the first year of follow-up data in ECLIPSE to establish an accurate 1-year history of exacerbation for each patient. Next, we used the second year of follow-up to validate the model. The model was validated first in the entire COPD cohort of ECLIPSE (n=1819) and then in a subset of patients with COPD who had at least one exacerbation in the first year of follow-up (n=996). This subset was similar to population characteristics of the development dataset, whereas the full ECLIPSE cohort enabled assessment of model generalisability beyond patients with exacerbation history.

We examined model calibration (degree to which predicted and actual risks or rates of exacerbations aligned) and discrimination (extent to which the model separated individuals with different risks).¹⁶ Calibration was assessed by comparing predicted and observed exacerbation rates across subgroups with differential risks, evaluating calibration plots, and calculating Brier scores (ie, mean squared error of forecast). Discrimination was assessed by calculating receiver operating characteristic (ROC) curves and the area-under-the-curve (AUC), and then comparing them using the DeLong's test.¹⁷ ROC and AUC calculations were based on occurrence of two or more exacerbations of any type or one or more severe exacerbations.³

The study was approved by the University of British Columbia and Providence Health Research Ethics Board (H11-00786).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AA, AS, DDS, and MS had full

	Rate component		Severity component	
	Estimate ln(HR) (95% CI)	p value	Estimate ln(OR) (95% CI)	p value
Intercept	-0.009 (-0.58 to 0.56)	0.97	-3.849 (-5.54 to -2.16)	<0.0001
Male vs female	-0.152 (-0.25 to -0.05)	0.003	0.377 (0.08 to 0.67)	0.01
Age at baseline (per 10 years)	-0.018 (-0.08 to 0.05)	0.58	0.109 (-0.07 to 0.29)	0.24
Current smoker at baseline	-0.195 (-0.32 to -0.07)	0.003	0.390 (0.03 to 0.75)	0.03
Oxygen therapy past year	0.085 (-0.03 to 0.20)	0.16	0.538 (0.20 to 0.88)	0.002
Baseline FEV ₁ (% of predicted)	-0.428 (-0.79 to -0.07)	0.02	-1.119 (-2.24 to 0.01)	0.05
SGRQ score† (per 10 units)	0.100 (0.07 to 0.13)	<0.0001	0.199 (0.11 to 0.29)	<0.0001
BMI (per 10 units)	-0.123 (-0.21 to -0.04)	0.004	-0.103 (-0.36 to 0.15)	0.43
CVD-indicated statins*	0.095 (-0.03 to 0.22)	0.13	0.315 (-0.03 to 0.67)	0.08
LAMA*	0.144 (0.03 to 0.25)	0.01	-0.134 (-0.45 to 0.18)	0.40
LABA*	0.118 (-0.01 to 0.24)	0.07	0.012 (-0.34 to 0.36)	0.95
ICS*	0.216 (0.09 to 0.34)	0.001	0.376 (0.03 to 0.72)	0.03
Random effect variance	0.60 (0.51 to 0.69)	<0.0001	2.385 (1.63 to 3.14)	<0.0001
Random effect covariance	0.147	0.17	..	..

All p values and 95% CIs were computed from the final Hessian matrix on the basis of t distribution with default degrees of freedom (number of patients minus number of random effects) using SAS NLMIXED, version 9.4. BMI=body-mass index. CVD=cardiovascular disease. FEV₁=forced expiratory volume in 1 s using Hankinson's method. ICS=inhaled corticosteroids. LABA=long-acting β agonist. OR=odds ratio. LAMA=long-acting muscarinic receptor antagonist. SGRQ=St George's Respiratory Questionnaire. *Binary predictor for medication use in past 12 months. †Between 0 and 100, with a higher score indicating worse status.

Table 2: Model coefficients for the joint rate-severity prediction model of COPD exacerbations

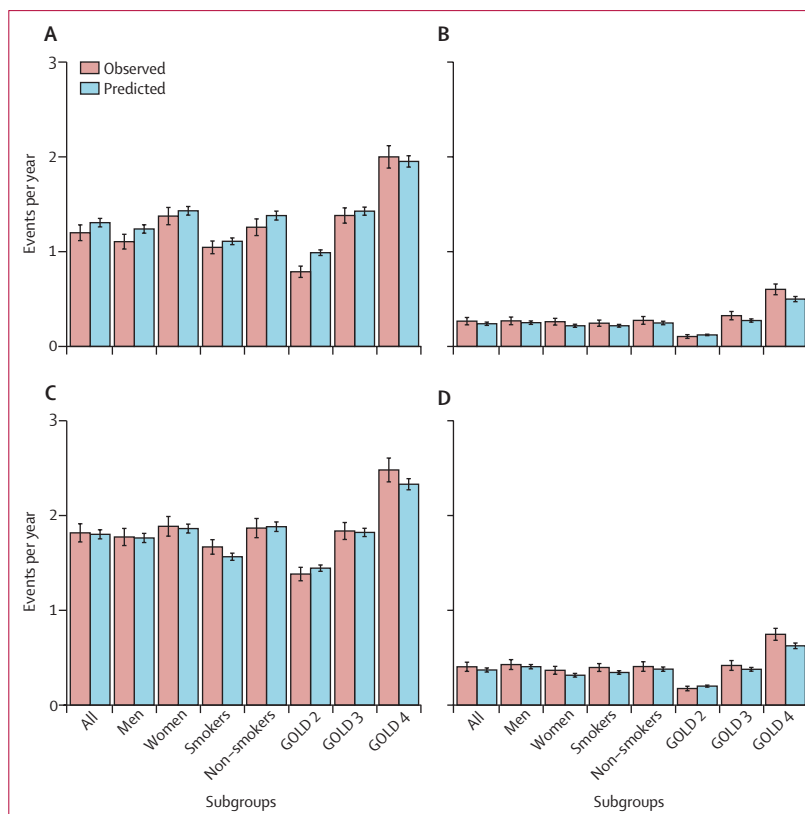


Figure 3: Calibration in risk-factor subgroups

Exacerbation rates (A) and severe exacerbation rates (B) in all patients with COPD, and exacerbation rates (C) and severe exacerbation rates (D) in patients with COPD and exacerbation history in the ECLIPSE study. GOLD=Global Initiative for Chronic Obstructive Lung Disease. ECLIPSE=Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points.

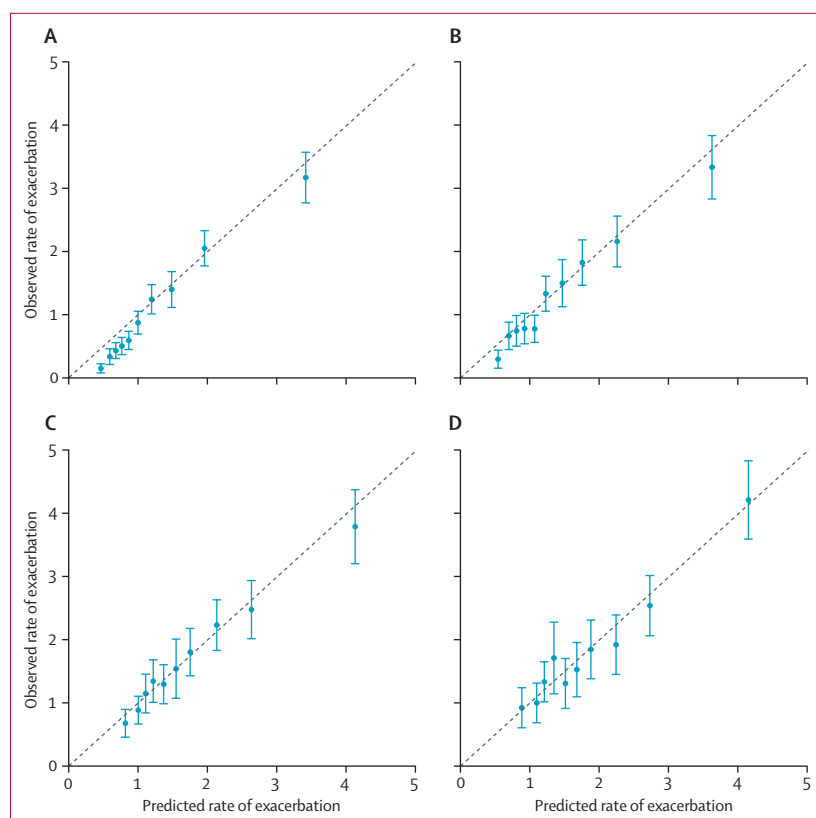


Figure 4: Calibration plot

Calibration plot comparing per decile average predicted and observed rate of exacerbations in (A) men with COPD (B) women with COPD and exacerbation history, and (D) women with COPD and exacerbation history in the external validation dataset in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points study. Perfect agreement is shown by the dashed line. Error bars represent 95% CI based on standard error of the mean.

access to all the data and had final responsibility for the decision to submit for publication.

Results

We excluded 96 patients who were lost to follow-up ($n=33$) or had missing values ($n=63$; figure 1). The final development dataset included 2380 patients (1107 from MACRO, 847 from STATCOPE, and 426 from OPTIMAL). Total mean age was 64.7 years (SD 8.8) and 1373 (58%) were men. Patients had a total of 3056 exacerbations, 628 of which were severe. In the external validation dataset, ECLIPSE, 109 patients had missing values. Thus, the final sample included 1819 patients with COPD (mean age was 63.3 years (SD 7.0), 1186 [65%] were men). Among these patients, 996 patients had at least one exacerbation in the first year (mean age was 63.6 years (SD 6.9), 611 [61%] were men). Figure 2 provides a detailed comparison of the development and validation datasets in terms of demographics, predictors, and outcome variables. Average exacerbation rates in the development dataset, validation set with all patients, and validation subset containing only those with previous history of an exacerbation was 1.42, 1.20, and 1.82 events per year,

respectively. For severe exacerbations, average rates were 0.29, 0.27, and 0.40 events per year, respectively.

The distribution of baseline predictors among different studies that were included in the development dataset is available in the appendix (pp 5–6). Notably, none of the participants in STATCOPE had a history of statin use because patients with cardiovascular comorbidities were excluded from this trial.

We assumed that missing values were missing at random and opted for a complete case analysis given that, after excluding patients who either did not have COPD or were lost to follow up, only 63 (3%) of 2443 patients in the combined development dataset and 109 (6%) of 1928 patients in the validation dataset had missing data (appendix p 6).

Table 2 provides coefficient estimates for predictors. Regression coefficients are shown as log-hazard ratios for the rate component and log-odds ratios for the severity component. Full regression results, including coefficients representing adjustments for treatment groups, are available in the appendix (p 8). Results remained largely unchanged in the secondary analysis based on placebo groups (appendix p 9).

When validated against all patients in ECLIPSE, regardless of exacerbation history, ACCEPT slightly overestimated their overall exacerbation rates (observed 1.20 events per year vs predicted 1.31 events per year; figure 3A) but was accurate for severe exacerbation rates (observed 0.27 events per year vs predicted 0.25 events per year; figure 3B). The same trend was observed in all subgroups with major risk-factors and in men and women (figure 3A–B, and figure 4A–B). The Brier score was 0.20 for all exacerbations and 0.12 for severe exacerbations. In patients with exacerbation history, ACCEPT showed robust overall calibration: predicted annual exacerbation rate closely matched observed rate for all exacerbations (observed 1.82 events per year vs predicted 1.80 events per year; figure 3C), severe exacerbations (observed 0.40 events per year vs predicted 0.37 events per year; figure 3D), and risk-factor subgroups (figures 3C–D). Calibration plots comparing per decile average rate of exacerbations showed good agreement between observed and predicted rates for men (figure 4C) and women (figure 4D). The Brier score was 0.17 for all exacerbations and 0.16 for severe exacerbations. Similar results for the development dataset are provided in the appendix (p 7).

In all patients with COPD, the model had an AUC of 0.81 (95% CI 0.79–0.83) for at least two exacerbations (figure 5A) and 0.77 (95% CI 0.74–0.80) for at least one severe exacerbation (figure 5B). Corresponding AUCs for patients with COPD with an exacerbation history were 0.73 (0.70–0.76) for two or more exacerbations (figure 5C) and 0.74 (0.70–0.78) for at least one severe exacerbation (figure 5D).

Compared with existing practice, which relies exclusively on previous history of exacerbation to predict

future risk of exacerbation, ACCEPT was better at predicting severe exacerbations in all patients with COPD ($AUC_{ACCEPT}=0.77$ vs $AUC_{event\ history}=0.66$; $p<0.0001$; figure 5B) and in those who had previous history of an exacerbation ($AUC_{ACCEPT}=0.74$ vs $AUC_{event\ history}=0.67$; $p<0.0001$; figure 5D). Similarly, ACCEPT showed better performance for all exacerbations regardless of severity (Figure 5A–C).

Discussion

The most important finding of the study was the development and validation of ACCEPT that uses simple and widely available clinical and demographic variables to predict risk and severity of exacerbations over a 12-month period, enabling personalisation of care for patients with COPD. ACCEPT was superior to using an individual's history of exacerbation to predict future risk of exacerbations and, in particular, for severe exacerbations (we observed an increase in AUC of 0.11 in all patients with COPD and 0.07 in those with an exacerbation in the previous year).

Although preventing exacerbations is a major goal in COPD care, no tools exist in practice that can accurately predict risk or rate of exacerbations in individuals. Studies suggest that patients with previous exacerbation history are more likely to exacerbate in the future than those without.² However, this approach is hampered by a relatively poor resolution, leading to large variations in risk across patients, even among those who have the same history of exacerbations. Our framework builds on this well accepted approach and extends its use by incorporating other clinical features that enable accurate prediction.

A 2017 systematic review of clinical prediction models for COPD exacerbations found that only two models^{18,19} of the 27 reviewed reported on any external validation. When availability of predictors and practical applicability were also considered, none of the models were deemed ready for clinical implementation.⁶ We are aware of only two additional prediction models^{20,21} published after this review that have reported external validation. ACCEPT has several notable advantages compared with these models. Importantly, ACCEPT is externally validated in an independent cohort extending its generalisability beyond therapeutic clinical trials. ACCEPT is also geographically generalisable because the external validation cohort contained data from 12 different countries across North America, Europe, and Oceania. By contrast, previous externally validated models used geographically limited datasets: CODEX was Spanish,¹⁸ Bertens and colleagues¹⁹ model was Dutch, Kerkhof and colleagues²⁰ model was British, and Annavarapu and colleagues²¹ model was based on cross-sectional administrative data from non-single-payer context in the USA. Bertens and colleagues model, CODEX, and models by Kerkhof and colleagues and Annavarapu and colleagues reported validation AUCs of 0.66, 0.59, 0.74, and 0.77, respectively. However, independence of the validation dataset in Kerkhof and

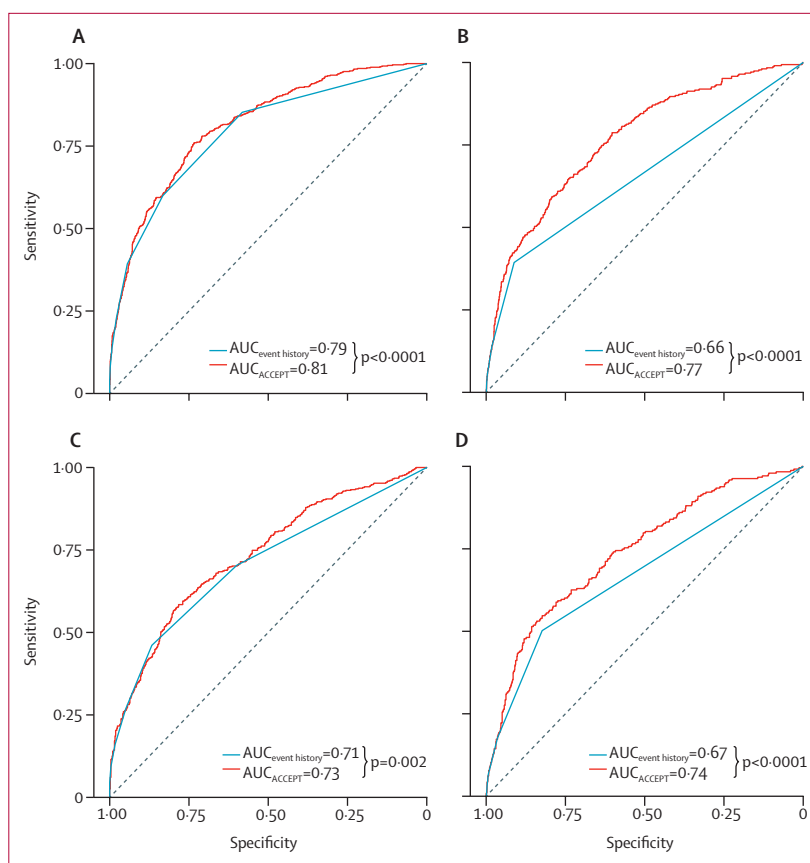


Figure 5: Discriminative ability of ACCEPT compared with event history

Receiver operating characteristic (ROC) curves of all patients with COPD with at least two exacerbations (A) and at least one severe exacerbation (B), and patients with COPD with exacerbation history with at least two exacerbations (C) and at least one severe exacerbation (D) in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study. In line with Global Initiative for Chronic Obstructive Lung Disease recommendations, area-under-the-curve (AUC) is shown for predicting at least two exacerbations and at least one severe exacerbation. DeLong's test for two correlated ROC curves was used to produce p values.

colleagues²⁰ model was questioned as it was selected from the same database as the developmental population. Annavarapu and colleagues²¹ did not report calibration. Overall, both models were not sufficiently generalisable given the local nature of data that were available to the investigators.

ACCEPT predicts rate and severity of exacerbations. This feature is crucial to appropriately tailoring treatments to an individual, as the granular nature of output in ACCEPT provides detailed prediction to assist clinicians in their decision making. For example, ACCEPT can predict the number of exacerbations at a given time period, time to next exacerbation, and probability of having a specific number of non-severe or severe exacerbations within a given follow-up time (up to 1 year). By contrast, logistic regression models, used in most previous clinical prediction models, predict the probability of having at least one exacerbation in a single timeframe.⁶ The ACCEPT framework can potentially be used for prognostic enrichment of randomised trials by identifying patients

who are likely to exacerbate. Similar to asthma trials, the required sample size and consequently the cost of large trials can be substantially reduced by using prediction models to recruit patients above a certain threshold of expected exacerbation rate.^{22,23}

ACCEPT can combine predicted risk with effect estimates from randomised trials to enable personalised treatment. For example, a benefit–harm analysis for roflumilast as preventive therapy for COPD exacerbations reported that benefits of roflumilast outweighed its potential harm when patients have severe exacerbation risk of at least 22% over a year.²⁴ Using data from this benefit–harm analysis, the accompanying web app of ACCEPT can be used to inform therapeutic decisions on use of roflumilast for a given patient. Another example is in the potential use of preventative daily azithromycin therapy in COPD. Azithromycin reduces annual exacerbation rate by 27%.⁸ However, this drug is associated with increased risk of hearing impairment and antimicrobial resistance and thus should be reserved for those at high risk of future exacerbations.⁸ The accompanying web app illustrates this application by showing risk of exacerbations with and without daily azithromycin therapy in a given patient. Once care providers discuss risks of harm and benefits of therapy and establish patient preference thresholds for benefit–harm tradeoff, ACCEPT can be used to determine whether preventive azithromycin therapy for that individual reaches or surpasses this threshold.

ACCEPT generates nuanced predictions that allow clinicians to accurately risk-stratify two patients, who have an identical exacerbation history. The case study in the appendix illustrates this feature by discussing two patients who have considerably different risk profiles (one projected to experience twice as many severe exacerbations as the other) despite an identical exacerbation history and similar medication profile, smoking status, and age (appendix p 2).

Several limitations must be noted. The pooled trial data we used to develop the model had insufficient data on certain variables, such as comorbidities, vaccination, blood markers (eg, eosinophil count), and socioeconomic status. As such, these predictors could not be incorporated into the model. Moreover, the developmental dataset did not contain individuals without exacerbations in the previous year; however, the model performed robustly in an external validation dataset that included such patients. Neither the developmental nor the validation datasets included patients with mild (GOLD 1) severity and, as such, we could not establish the accuracy of predictions for this subgroup. Additionally, our model might not be generalisable to patients with COPD with a history of asthma, lifetime non-smokers, patients younger than 40 years or older than 80 years, or populations outside North America, Europe, and Oceania. Model updating and re-examination of its external validity will be necessary when new sources of data become available.²⁵

Compared with simple scoring systems, such as the BODE index that can be manually calculated, ACCEPT requires sophisticated computational analysis. Although parsimonious models are useful at the bedside, given the complexity of processes involved in the pathogenesis of COPD exacerbations, we believe such tools will have inadequate resolution. Given the proliferation of hand-held computational devices in clinical practice and the wide availability of clinical parameters that are contained in the model, ACCEPT is usable clinically. Such use is facilitated through its availability as a web app, spreadsheet, and the R package, “accept”.²⁶

We emphasise that estimates in our model are predictive and should not be interpreted as causal. The observed association between being a smoker and low exacerbation rate (hazard ratio 0.82 [95% CI 0.73–0.93]) is one such example. Smoking is likely a marker of disease severity with sick patients less likely to smoke than those with mild disease. As such, information in the smoking status variable has high predictive value for tendency towards exacerbation but is not causally interpretable.

ACCEPT is an externally validated and generalisable prediction model that enables nuanced prediction of the rate and severity of exacerbations and provides individualised estimates of risks and uncertainty in predictions. ACCEPT has good to excellent discriminatory power in predicting rate and severity of COPD exacerbations in all patients with COPD and showed robust calibration in individuals with history of such exacerbations in the past year. Objective prediction of outcomes given each patient’s unique characteristics can help clinicians to tailor treatment of patients with COPD on the basis of their individualised prognosis.

Contributors

MS, DDS, JMF, and SDA conceived the study. AA, AS, and MS developed and validated the model. DDS and SDA contributed to data acquisition. AA, KMJ, AS, JMF, DDS, SDA, and MS contributed to interpretation of the data. AA wrote the first draft of the manuscript and created data visualisations. JMF, DDS, SDA, and MS provided clinical input and oversight. AA developed the web application with crucial input from KMJ, SDA, DDS, and MS. MS and AA developed the interactive spreadsheet and R package. All authors revised the manuscript critically and approved the final version to be published.

Declaration of interests

We declare no competing interests.

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For R package see
[https://CRAN.R-project.org/
 package=accept](https://CRAN.R-project.org/package=accept)

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