Development and External Validation of the Acute COPD Exacerbation Prediction Tool (ACCEPT)

Amin Adibi, MSc[1]; Don D Sin, MD[2]; Abdollah Safari, PhD[1]; Kate M Johnson, MSc[1]; Shawn D Aaron, MD[5], J Mark FitzGerald, MD[3,4]; Mohsen Sadatsafavi, MD, PhD[1,3,4]

Affiliations:

[1] Respiratory Evaluation Sciences Program, Faculty of Pharmaceutical Sciences, University of British Columbia, 2405 Wesbrook Mall, Vancouver, British Columbia, Canada V6T 1Z3.

[2] Division of Respiratory Medicine, Department of Medicine, The UBC Centre for Heart Lung Innovation, St. Paul's Hospital, University of British Columbia, 1081 Burrard Street, Vancouver, British Columbia, Canada V6Z 1Y6

[3] Institute for Heart and Lung Health, Division of Respiratory Medicine, Faculty of Medicine, University of British Columbia, 7th Floor, 2775 Laurel Street, Vancouver, British Columbia, Canada V5Z 1M9

[4] Centre for Clinical Epidemiology and Evaluation, University of British Columbia, 828 West 10th Avenue, Vancouver, BC, Canada, V5Z 1M9

[5] Ottawa Hospital Research Institute, University of Ottawa, Ontario, Canada K1H 8L6

Corresponding author: Don Sin, MD[2]

Division of Respiratory Medicine, Department of Medicine, The UBC Centre for Heart Lung Innovation, St. Paul's Hospital, University of British Columbia, 1081 Burrard Street, Vancouver, British Columbia, Canada V6Z 1Y6

Phone: (604) 806-8346 x68395

E-mail: Don.Sin@hli.ubc.ca

Conflict of interest:

Funding source: CIHR Catalyst Grant (#155554)

Abstract word count (Max 250): 250 words

Main text word count (excluding title page, abstract, references, tables, figures, statements): 3487 words

Number of tables: 4

Number of figures: 4

Number of references: 25

Number of appendices: 4

Keywords: COPD, exacerbation, clinical prediction model, prognosis, precision medicine

Research in context

Evidence before this study: A 2017 systematic review reported that of the 27 identified COPD exacerbation prediction tools, only two had reported external validation and none was ready for clinical implementation. To find the studies that were published afterwards, we searched PubMed for articles on development and validation of COPD exacerbation prediction since 2015, using the search terms "COPD", "exacerbation", "model", and "validation". We included studies that reported prediction of either the risk or the rate of exacerbations and excluded studies that did not report external validation.

Added value of this study: ACCEPT is the first COPD exacerbation prediction tool that jointly estimates the individualised rate and severity of exacerbations. ACCEPT is externally validated, generalisable, and readily accessible.

Implications of all the available evidence: The availability of an individualised exacerbation risk can enable patients and care providers to decide on preventive therapies based on patient-specific, objectively-established thresholds for treatment benefit.

Abstract

Background: Risk prediction tools enable precision medicine. However, most tools to predict COPD exacerbations do not fulfil established criteria for personalising care. We developed and validated an accessible tool to predict the individualised rate and severity of COPD exacerbations.

Methods: We pooled data from three COPD trials on patients with a history of exacerbations. We developed a mixed-effect model to predict exacerbations over one-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. ECLIPSE, a multicentre cohort study, was used for external validation.

Results: The development dataset included 2,380 patients (mean 64·7 years, 57·7% men, mean exacerbation rate 1·42/year, 20·5% severe). When validated against all COPD patients in ECLIPSE (n=1819, mean 63·3 years, 65·2% men, mean exacerbation rate 1·20/year, 22·2% severe), the area-under-curve was 0·81 (95%CI 0·79–0·83) for ≥2 exacerbations and 0·77 (95%CI 0·74–0·80) for ≥1 severe exacerbation. Predicted annual exacerbation rates (1·31) slightly overestimated observed rates (1·20). In ECLIPSE patients with prior exacerbation history (n=996, mean 63·6 years, 61·3% men, mean exacerbation rate 1·82/year, 22·0% severe), mean predicted annual exacerbation rates (1·80) matched observed rates (1·82). Area-under-curve was 0·73 (95%CI 0·70–0·76) for ≥2 exacerbations and 0·74 (95%CI 0·70–0·78) for ≥1 severe exacerbation. The model is accessible at http://resp.core.ubc.ca/ipress/accept.

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

Funding: Canadian Institutes of Health Research (Grant #155554).

1. Background and Objectives

Chronic Obstructive Pulmonary Disease (COPD) is usually manifested by an accelerated loss of lung function, presence of chronic respiratory symptoms, and periods of intensified disease activity commonly referred to as exacerbations.[1] COPD is known to be a heterogeneous disorder with large variations in the risk of exacerbation across patients.[2] In clinical practice, a history of two or more moderate exacerbations and one severe exacerbation per year is used frequently to guide therapeutic choices for exacerbation prevention.[3] Although the use of this historical variable improves the risk-benefit profile of therapeutic interventions, there remains a significant amount of heterogeneity within the high-exacerbator group.[4]

Prognostic clinical prediction tools enable personalised approaches to disease management. Despite potential benefits, no such tool is routinely used in the management of COPD. This is unlike COPD-related mortality for which clinical scoring schemes such as the BODE index are routinely used.[5] A 2017 systematic review by Guerra and colleagues identified 27 prediction tools for COPD exacerbations.[6] Among these, only two reported on the validation of the model and none were deemed ready for personalised COPD management in the clinic.[6]

Our goal here was to build upon previous modelling efforts by developing and validating the Acute COPD Exacerbation Prediction Tool (ACCEPT). ACCEPT predicts both the frequency (rate) of exacerbations and their severity, incorporates individual variability beyond model predictors, and is clinically applicable and easily accessible. As a decision tool, ACCEPT provides a personalised risk profile that allows clinicians to more objectively communicate risks with patients and tailor treatment regimens to their individual needs.

2. Methods

In reporting our prediction model, we have followed recommendations set forth by the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement.[7]

Target population and source of data

We developed the model using data from COPD patients who had experienced at least one exacerbation within the preceding 12 months and were not diagnosed with asthma. We externally validated the model in two populations: 1) all COPD patients regardless of exacerbation history, and 2) COPD patients with at least one exacerbation within the preceding 12 months.

We pooled data across all arms of three randomised controlled trials: Macrolide Azithromycin to Prevent Rapid Worsening of Symptoms in COPD (MACRO)[8], Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD (STATCOPE)[9], and Optimal Therapy of COPD to Prevent Exacerbations and Improve Quality of Life (OPTIMAL)[10] to create the development dataset. We used ECLIPSE[11] – an independent longitudinal COPD cohort – for external validation. The details of each of these studies have been previously published. Briefly, the MACRO study[8] evaluated the effect of daily low-dose azithromycin therapy on the rate of exacerbations in COPD patients; the STATCOPE study evaluated the effects of daily simvastatin therapy on the rate of exacerbation[9], and the OPTIMAL study evaluated the effects of tiotropium-fluticasone-salmeterol on the rate of exacerbation compared with tiotropium-fluticasone and tiotropium alone.[10] In all three trials, which comprised the development dataset, study patients reported a history of at least one exacerbation over the previous 12 months. ECLIPSE was a multicentre three-year observational study aimed at characterising COPD phenotypes and identifying markers of disease progression.[11] *Table 1* provides a detailed summary of these studies.

<<Table 1>>

Outcomes

The outcomes of interest were the rates of all exacerbations and severe exacerbations over one year. Exacerbations were the primary outcome of all three trials, and a major outcome measure of the ECLIPSE study. We harmonized the definition of exacerbations among trials based on the criteria endorsed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[3] An exacerbation was defined as an acute episode of intensified symptoms that requires additional therapy.[3] Mild exacerbations were defined as exacerbations treated with short-acting bronchodilators only. Moderate exacerbations were defined as periods of sustained worsening of symptoms requiring the institution of systemic corticosteroids and/or antibiotics. Severe exacerbations were defined as exacerbations requiring an emergency department visit or hospitalisation.[3,8–10] Number of all exacerbations was defined as the total number of mild, moderate, and severe exacerbations.

Predictors

Predictors were chosen *a priori* based on clinical relevance and availability of predictor in all datasets. They consisted of the number of non-severe and severe exacerbations over the previous year, baseline age, sex, smoking status, use of domiciliary oxygen therapy, percent predicted post-bronchodilator forced expiratory volume in one second (FEV_1 % predicted[12]), St. George's respiratory questionnaire (SGRQ) score, body mass index (BMI), and the use of COPD and non-COPD medications during the previous 12 months. The medication list included long-acting muscarinic receptor antagonists (LAMAs), long-acting

β2 agonists (LABAs), inhaled glucocorticoids (ICS), and statins. In addition to baseline medications, the treatments to which patients were randomised to during the trials (azithromycin in MACRO; statins in STATCOPE; LABA/LAMA and ICS in OPTIMAL) were included in the model to adjust for their potential effects but were not included for prediction.

To facilitate clinical implementation, the web application allows user to enter COPD Assessment Test (CAT) score instead of SGRQ, which was converted to SGRQ using published data.[13]

Follow up

We applied administrative censoring at the one-year follow-up time for patients who had data beyond year one. The decision to limit predictions to one year was made *a priori* based on the assumption that predicting exacerbations over the next year was the most relevant for clinical COPD management, and that prediction accuracy would decrease substantially beyond one year. Finally, the one year prediction period, as opposed to a shorter time span, also mitigated the seasonal effects on predictions.

Statistical analysis methods

We used a joint accelerated failure time and logistic model to characterise the rate and severity of exacerbations. We have previously published the details of this approach elsewhere.[14] In summary, this framework assigns two random-effect terms to each individual, enabling between-individual variability and quantifying each individual's specific tendency towards a particular rate of exacerbations and the probability that once an exacerbation occurs, it will be severe (*Supplementary Appendix I*). For each patient, this framework fully specifies the hazard of all and severe exacerbations at any given point during follow-up, allowing nuanced predictions such as the probability of having any exacerbations or a specific number of total and severe exacerbations during the next twelve months.

Two forms of uncertainty in predictions were quantified: the uncertainty due to the finite sample of the validation set (represented by the 95% confidence interval [95%CI] around the mean of projected values), and uncertainty due to the 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 given the relatively high events per predictor in the development dataset.[15] Because in this framework, the correlation between the previous and future exacerbations rates is modelled through random-effect terms, previous history of exacerbation does not enter the model as a predictor. Instead, a Bayesian approach is employed to update the distribution of future exacerbation rate and severity given exacerbation history

(*Supplementary Appendix II*). The availability of full exacerbation history in the external validation cohort enabled evaluating the validity of this approach.

External validation

In the ECLIPSE study, we used exacerbation data from the second year of follow-up for model validation and the data for the first year to establish exacerbation history. We used ECLIPSE to create two validation datasets that included: 1) all COPD patients (n=1,819), and 2) COPD patients with at least one exacerbation in the first year of follow-up (n=996). The second validation set was similar to the target population of the development dataset, while the first one enabled assessment of generalisability of the model beyond patients with an exacerbation history.

We examined both model calibration (the degree by which predicted and actual risks or rates are aligned) and model discrimination (the extent to which the model can separate individuals with different risks).[16] Model calibration was assessed through comparing the predicted and observed exacerbation rates among risk-factor subgroups, evaluating calibration plots, and the Brier score. Model discrimination was assesses by the receiver operating characteristic (ROC) curve, and the area-under-the-curve (AUC). In line with clinically important thresholds in GOLD guideline, ROC and AUC calculations were based on the occurrence of two or more exacerbations of any type, or one or more severe exacerbations.[3] Correlated ROC curves were compared using DeLong's test.[17]

Ethics Approval

The study was approved by Providence Health Research Ethics Board (H11-00786).

3. Results

Participants

Figure 1 presents the flowchart of sample selection. We excluded 96 patients who were either lost to follow-up (n=33) or had missing values (n=63). The final development dataset included 2,380 patients (1,107 from MACRO, 847 from STATCOPE, and 426 from OPTIMAL; overall mean age 64.7, 57.7% male). Patients experienced a total of 3,056 exacerbations, 628 of which were severe. In the external validation dataset, ECLIPSE, 109 patients had missing values and 823 patients did not have an exacerbation history; the final sample included 1,819 COPD patients (mean age 63·3, 65·2% male). Among these 996 COPD patients had at least one exacerbation in the first year (mean age 63·6, 61·3% male). *Table 2* provides a detailed comparison of the development and validation datasets, in terms of demographics, predictors, and outcomes variables.

<<Figure 1 and Table 2>>

Supplementary Appendix III – Table S1 shows the distribution of baseline predictors among different studies that were included in the development dataset. Most predictors had similar distributions among the three trials with a few exceptions: none of STATCOPE participants had a history of statin use because patients with cardiovascular co-morbidities were excluded from this trial; a smaller proportion of OPTIMAL patients used oxygen therapy or LABAs than in STATCOPE; and the proportion of patients on ICS was lower in STATCOPE.

We assumed that missing values were missing at random and opted for a complete case analysis given that only 2·58% of patients in the combined development dataset and 5·65% of patients in the validation dataset had missing data (*Supplementary Appendix III – Tables S2 and S3).*

Model specification and performance

Table 3 provides coefficient estimates for predictors. Regression coefficients are shown as log-hazard ratios (ln-HR) for the rate and log-odds rations (ln-OR) for the severity.

<<Table 3>>

ACCEPT showed robust overall calibration (i.e. calibration-in-the-large) in patients with exacerbation history: predicted annual exacerbation rate closely matched the observed rate for all exacerbations (observed 1·82 events/year, predicted 1·80 events/year), severe exacerbations (observed 0·40 events/year, predicted 0·37 events/year), and risk-factor subgroups (*Figure 2B).* Calibration plots comparing per decile average rate of exacerbations showed good agreement between observed and predicted rates for both female and male patients (Figure 4*B*). Brier score was 0·17 for all exacerbations and 0·16 for severe exacerbations. When validated against all COPD patients in ECLIPSE, ACCEPT slightly overestimated overall exacerbation rates (observed 1·20 events/year, predicted 1·31 events/year) but was fairly accurate for severe exacerbation rates (observed 0·27 events/year, predicted 0·25 events/year, *Figure 2A*). The same trends was observed in major risk-factor subgroups (Figure 4*A).* Brier score was 0·20 for all exacerbations and 0.12 for severe exacerbations. Similar results for the development dataset are provided in *Supplementary Appendix IV*.

In all COPD patients, the model had an AUC of 0·81 (95%CI 0·79–0·83) for ≥2 exacerbations and 0·77 (95%CI 0·74–0·80) for ≥1 severe exacerbation (Figure 4*A)*. Corresponding AUCs for COPD patients with exacerbation history 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 (Figure 4*B)*.

Compared with current standard practice of relying on exacerbation history for predicting future exacerbation, ACCEPT improved prediction of severe exacerbations in all COPD patients (AUC_{ACCEPT}=0·77 vs. $AUC_{Event\ History}$=0·66, p<0·0001) as well as those with exacerbation history (AUC_{ACCEPT}=0·74 vs. $AUC_{Event\ History}$=0·67, p<0·0001). Similarly, ACCEPT showed an improved discrimination performance in all COPD patients in both external validation sets (Figure 4).

<<Figure 2, Figure 3, Figure 4>>

4. Discussion

While preventing exacerbations is a major goal in COPD care, no good tool to date accurately predicts the rate of exacerbations in a given individual. Prior studies suggest that patients with a prior history of an exacerbation are more likely to exacerbate in the future than those without. However, clinical usability of the past history of exacerbations is hampered by a relatively poor resolution, leading to large variations in risk across and within subjects even with the same history of exacerbations. Our framework builds upon this well-accepted predictor and can be used as a complement to this rule-of-thumb. We used pooled data from three clinical trials to show that a model containing simple clinical and demographic variables in aggregate can be used to predict the risk of exacerbation with improved accuracy over 12 months of follow-up.

A 2017 systematic review of clinical prediction models for COPD exacerbations found that only two of the 27 reviewed models – CODEX[18] and Bertens' model[19] – reported on any external validation. When the availability of predictors and practical applicability were also taken into account, none of the models were deemed ready for clinical implementation.[6] Aside from these, we are aware of only two additional prediction models – by Kerkhof[20] and Annavarapu[21] – that have reported external validation. ACCEPT has several notable advantages over previously published COPD exacerbation models. Importantly, it was externally validated in an independent cohort extending its generalisability beyond therapeutic trials to the "real-world". It is reassuring that ACCEPT is generalisable across geographical settings, given that the external validation covered 12 countries within North America, Europe, and Oceania. In contrast, previous externally validated exacerbation models used geographically limited datasets: CODEX was Spanish[18], Bertens' model was Dutch[19], Kerkhof's model was British[20], and Annavarapu's model was based on cross-sectional data from an administrative dataset in the non-single-payer context of the United States.[21] ACCEPT provides reasonable discrimination and robust calibration in external validation. In comparison, Bertens' model and CODEX reported validation AUCs of 0·66 and 0·59, respectively. Models by Kerkhof and Annavarapu reported AUCs of 0·74 and 0·77, respectively. However, the independence of the validation dataset in Kerkhof's model was questionable as it was selected from the

same database as the development population, Annavarapu did not report calibration at all, and overall, both models suffered from a lack of generalisability given the local nature of the data that were available to the investigators.

ACCEPT predicts the rate and severity of exacerbations jointly. This is critical to appropriately tailoring the treatment to an individual, as the more granular nature of the output in ACCEPT provides more 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 the probability of experiencing a specific number of non-severe or severe exacerbations within a given follow-up time (up to one year). This is in contrast to the logistic regression models used in the majority of previous clinical prediction models, as they only predict the probability of having at least one exacerbation in a single time window.[6]

Further, this framework can potentially be used for prognostic enrichment of randomized trials by identifying patients who are more 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]

Example of Application in Clinic

ACCEPT can combine predicted risk with effect estimates from randomised trials to enable personalised treatment. For example, a harm-benefit analysis for roflumilast as preventive therapy for COPD exacerbations has shown that the benefits of roflumilast outweigh potential harm when the patient has a severe exacerbation risk of at least 22% within a year.[24] To showcase the capacity of informing treatment decisions based on such benefit-risk analyses, the accompanying web app makes a recommendation for roflumilast based on whether the patient meets this threshold. Another example is preventative daily azithromycin therapy. Azithromycin is shown to decrease exacerbation rate by 27%.[8] However, it is associated with increased risk of hearing impairment and potential for antimicrobial resistance and thus should be reserved for those at a high risk of future exacerbations.[8] The accompanying web app illustrates this application by showing the risk and the rate of exacerbations with and without daily azithromycin therapy. The individualised estimate of benefit from preventive azithromycin therapy can be juxtaposed against risks of harm and patient preferences for benefit/harm trade-off, to decide on whether preventive azithromycin therapy is warranted.

<<Table 4>>

ACCEPT is able to make nuanced predictions that allows clinicians to differentiate between patients who have a similar exacerbation history. Consider Patient A, an ex-smoker 57-year-old male with the chronic bronchitis phenotype, an FEV1 of 51% of the predicted value (GOLD 2), a BMI of 18, and a CAT score of 29. Now consider Patient B, a 57 years old female ex-smoker with the chronic bronchitis phenotype, an FEV1 of 75% (GOLD 2), a CAT score of 10, and a BMI of 30. Both patients had two exacerbations within the past year, one of which was severe and they both were on LAMA, LABA, and ICS, but not statins.

Complete baseline characteristics of the two patients and ACCEPT predictions are shown in Table 4. ACCEPT predicts severe exacerbation probabilities of 29% and 18% and severe exacerbation rates of 0.6 and 0.3 events/year for Patients A and B, respectively. Patient A is 1.6 times more likely as Patient B to exacerbate severely and will likely incur twice as many severe exacerbations as Patient B, even though both patients have the same exacerbation history, GOLD stage, and smoking status.

Additionally, by combining the risk profile with harm-benefit analysis for Roflumilast[24], the web app for ACCEPT predicts that roflumilast will provide a net benefit to Patient A (net benefit probability>80%) but will likely do more harm than good for Patient B (net benefit probability<20%).

Limitations

The pooled trial data we used to develop the model lacked complete data on variables such as comorbidities, vaccination, blood markers (e.g. eosinophil count), and socio-economic status. As such, these predictors could not be incorporated into the model. The development dataset did not contain individuals without exacerbations in the previous year, however, the model performed robustly in external validation dataset that included such patients. The model was well-calibrated to predict severe exacerbations, but slightly overestimated the rate of non-severe exacerbations, especially in men. The exacerbations were well-calibrated in all subgroups of patients with a history of exacerbation. Our model may not be generalisable to COPD patients with a history of asthma, lifetime non-smokers, patients younger than 40 and older than 80, and 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 to simple scoring systems such as the BODE index that can be manually calculated, ACCEPT requires relatively sophisticated computation. We believe the inclination towards simplifying risk estimation to facilitate accessibility should not sacrifice predictive accuracy. Instead, ACCEPT is made accessible and ready for clinical and research applications through a web app, a spreadsheet, and an R package.

We also emphasise that predictor effect estimates in our model are predictive and should not be interpreted as causal. The observed association between being a smoker and a having a lower 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 sicker patients less likely to smoke than those with milder disease. As such, the information in the smoking status variable has high predictive value for the tendency towards exacerbation but is not causally interpretable. Similarly, medication history is a surrogate measure of disease activity or the burden of cardiovascular comorbidities; as such, their association with the outcome does not represent their causal effect

How to Access the Model

An easy-to-use web application for ACCEPT is available at http://resp.core.ubc.ca/ipress/accept. For any individual patient, the web app predicts multiple outcomes including 1) the exacerbation risk within the next 12 months, 2) the predicted annual rate of exacerbations, and 3) the probability of experiencing any given number of exacerbations. All outcomes are reported separately for overall and severe exacerbations.

Additionally, we provide an open-source R package, a spreadsheet template, public application programming interfaces (APIs), and additional code at http://resp.core.ubc.ca/research/Specific_Projects/accept.

5. Conclusions

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 had reasonable discriminatory power in predicting the rate and severity of COPD exacerbations in all COPD patients and showed robust calibration in individuals with a 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 COPD patients based on their individualised prognosis. In many other disciplines, objective risk prediction has become a cornerstone of disease management. As our understanding of disease mechanisms advances, frameworks of this type can be further improved to enable shared, informed decision making between patients and care providers.

Acknowledgment

We would like to thank co-investigators Janet Sutherland, Kelly Ablog-Morrant, Drs. Larry Lynd, Teresa To, Annalijn Conklin, Wenjia Chen, Laura Nimmon, Iraj Poureslami, and Hui Xie for their input and feedback.

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 the interpretation of the data. AA wrote the first draft of the manuscript and created data visualizations. JMF, DDS, SDA, and MS provided clinical input and oversight. AA developed the Web Application with critical input from KMJ, SDA, DDS, and MS. MS and AA developed the interactive spreadsheet. All authors revised the manuscript critically and approved the final version to be published.

Declaration of Interest

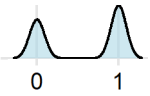
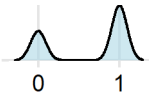
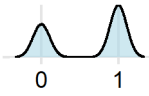
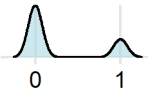
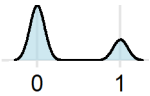
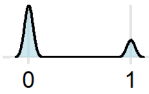
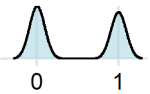
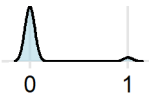
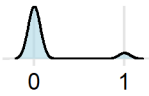
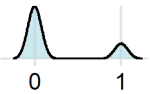
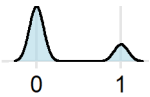
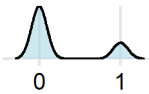
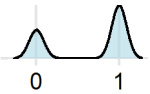
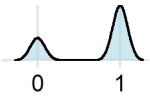
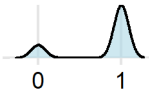
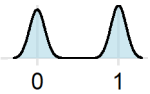
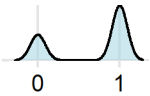
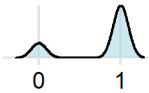
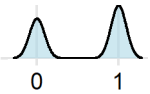
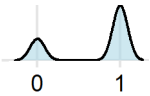
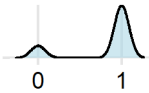
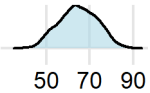
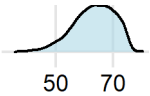
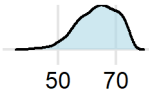
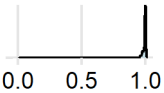
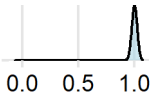
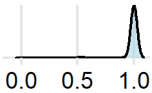
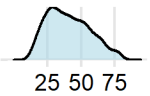
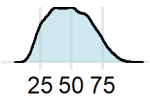
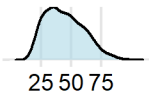
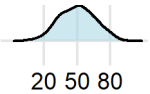
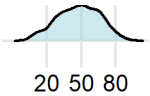
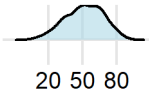
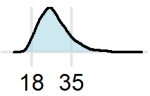
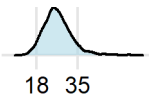
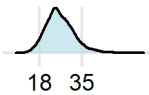
Authors declare no conflicts of interest.

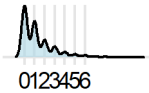
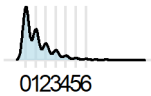
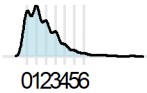
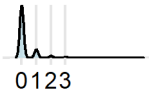
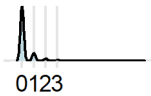
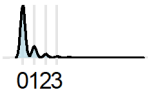
Table 1 Available datasets with data on the rate, time, and severity of COPD exacerbations.

Data Source	Design	Intervention	Study Period (Follow-up)	Centres	Inclusion Criteria	Exclusion Criteria
Development						
MACRO	Randomized trial	Azithromycin	03-2006 to 07-2010 (1 year)	17 sites in US	>40 yr. Clinical diagnosis of COPD. >10 pack-years of smoking. O_2 or systemic glucocorticoids therapy in the last yr. Hospitalization or ER visit.	Asthma. Exacerbation in the last month. HR above 100 /min. QT_C >450ms. QT_C prolonging or TdP-related medication except for amlodipine. Hearing impairment.
STATCOPE	Randomized trial	Simvastatin	03-2010 to 01-2014 (~2 years)	45 sites (29 in US and 16 in Canada)	40-80 yrs. Clinical diagnosis of COPD. >10 pack-years of smoking. O_2 OR systemic glucocorticoids OR antibiotics therapy OR hospitalization OR ER visit in the last yr.	Asthma. Receiving statins, or should have received statins. On drugs that contradicted with statins. Unable to take statins. Active liver disease, alcoholism, or allergy.
OPTIMAL	Randomized trial	Tiotropium in combination with Salmeterol or Fluticasone-Salmeterol	10-2003 to 01-2006 (1 year)	27 sites in Canada	>35 yr. Clinical diagnosis of COPD. >10 pack-years of smoking. Exacerbation requiring systemic glucocorticoids OR antibiotics therapy in the last yr.	Asthma <40 yrs. CHF with persistent severe LVD. 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		12-2005 to 02-2010 (3 years)	46 sites in 12 countries	40-75 yrs. Clinical diagnosis of COPD. >10 pack-years of smoking.	Respiratory disorders other than COPD. Reported exacerbation in the past month. Significant inflammatory disease.

[a] The number of patients and exacerbation events mentioned here reflect those from the raw dataset from each study, before any exclusions. Number of patients and events in the final development and validation datasets in presented in Table 2.

Table 2 Comparison of the Final Development and Validation Datasets

Predictor	Development (n=2380)		Validation (n=1819)	All COPD Patients	Validation (n=996)	COPD Patients with Event History
	%	Distribution	%	Distribution	%	Distribution
Male Sex	57·69		65·20		61·28	
Current Smokers	25·80		27·49		25·48	
O_2 therapy previous year	46·85		6·87		10·23	
On statins	22·65		23·58		23·07	
On LAMA	65·04		70·97		80·54	
On LABA	52·06		68·78		78·54	
On ICS	57·23		71·69		81·34	
	Mean (SD)	*Distribution*			*Mean (SD)*	*Distribution*
Age, years	64·68 (8·75)		63·30 (6·99)		63·53 (6·90)	
Follow–up time, years	0·90 (0·23)		0·97 (0·12)		0·97 (0·13)	
FEV_1, % predicted	40·60 (15·93)		48·40 (16·39)		44·60 (15·88)	
SGRQ Score[b]	49·95 (16·72)		47·41 (18·22)		51·43 (17·03)	
BMI	27·53 (6·44)		26·55 (5·80)		26·21 (5·77)	
Rate of Exacerbations[c]	Rate	Distribution	Rate	Distribution	Rate	

Total	1·42		1·20		1·82	
Severe/very severe	0·29		0·27		0·40	

Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta antagonist; ICS, inhaled corticosteroids; FEV1, % predicted forced expiratory volume in 1 second using Hankinson's method[12]; SGRQ, St. George's Respiratory Questionnaire; BMI, body mass index.

[a] Data are presented as mean (SD) for continuous predictors and number of subjects (% of column total) for dichotomous predictors, except where noted.

[b] Between 0 and 100, with a higher score indicating worse status.

[c] Numbers in the % column show the annual rate of exacerbations (episodes/patient).

[d] Number of participants with the specified number of COPD exacerbations during follow–up.

Table 3 Model coefficients for the Joint Rate–Severity Prediction Model of COPD Exacerbations [a]

Predictor	Rate Component			Severity Component		
	Estimate ln(HR)	95%CI	p	Estimate ln(OR)	95%CI	p
Intercept	-0·009	-0·58, 0·56	0·974	-3·849	-5·54, -2·16	<·0001
Male	-0·152	-0·25, -0·05	0·003	0·377	0·08, 0·67	0·012
Age at baseline (per 10–year)	-0·018	-0·08, 0·05	0·576	0·109	-0·07, 0·29	0·240
Current smoker [b] at Baseline	-0·195	-0·32, -0·07	0·003	0·390	0·03, 0·75	0·034
Oxygen therapy [b] last year	0·085	-0·03, 0·2	0·162	0·538	0·2, 0·88	0·002
Baseline FEV_1 (% predicted)	-0·428	-0·79, -0·07	0·020	-1·119	-2·24, 0·01	0·051
SGRQ Score [c] (per 10–unit)	0·100	0·07, 0·13	<·0001	0·199	0·11, 0·29	<·0001
BMI (per 10–unit)	-0·123	-0·21, -0·04	0·004	-0·103	-0·36, 0·15	0·434
CV-indicated statins [b]	0·095	-0·03, 0·22	0·127	0·315	-0·03, 0·67	0·078
LAMA [b]	0·144	0·03, 0·25	0·011	-0·134	-0·45, 0·18	0·402
LABA [b]	0·118	-0·01, 0·24	0·066	0·012	-0·34, 0·36	0·946
ICS [b]	0·216	0·09, 0·34	0·001	0·376	0·03, 0·72	0·034
Random Effect Variance	0·60	0·51, 0·69	<·0001	2·385	1·63, 3·14	<·0001
Random Effect Covariance	0·147		0·172			

Abbreviations: CI, confidence interval; FEV1, % predicted forced expiratory volume in 1 second using Hankinson's method[12];; SGRQ, St. George's Respiratory Questionnaire; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta antagonist; ICS, inhaled corticosteroids; BMI, body mass index.

[a] All p–values and confidence limits were computed from the final Hessian matrix
based on a t distribution with default degrees of freedom (number of subjects minus number of random effects) in SAS NLMIXED.

[b] Binary predictor for medication use in the previous 12 months.

[c] Between 0 and 100, with a higher score indicating worse status.

Table 4 Case study: Despite having the same exacerbation history, predicted severe exacerbation rate and risk for patients A is almost twice as patient B leading to different recommendation for roflumilast therapy.

Predictor	**Patient A**	**Patient B**
Gender	Male	Female
Age	57	57
Current smoker	No	No
Oxygen therapy last year	No	No
FEV_1 (% predicted)	51 (GOLD 2)	75 (GOLD 2)
CAT Score	29	10
BMI	18	30
CV-indicated statins	No	No
LAMA	Yes	Yes
LABA	Yes	Yes
ICS	Yes	Yes
Exacerbations in the last year	2	2
Severe Exacerbations in the last year	1	1
Predictions	**Patient A**	**Patient B**
Predicted Exacerbation Risk	%82	%79
Predicted Severe Exacerbation Risk	%28	%18
Predicted Exacerbation Rate	2.1	1.9
Predicted Severe Exacerbation Rate	0.6	0.3
Chance of Net Benefit from Roflumilast	80%-90%	10%-20%
Roflumilast Prescription	Recommended	Not Recommended

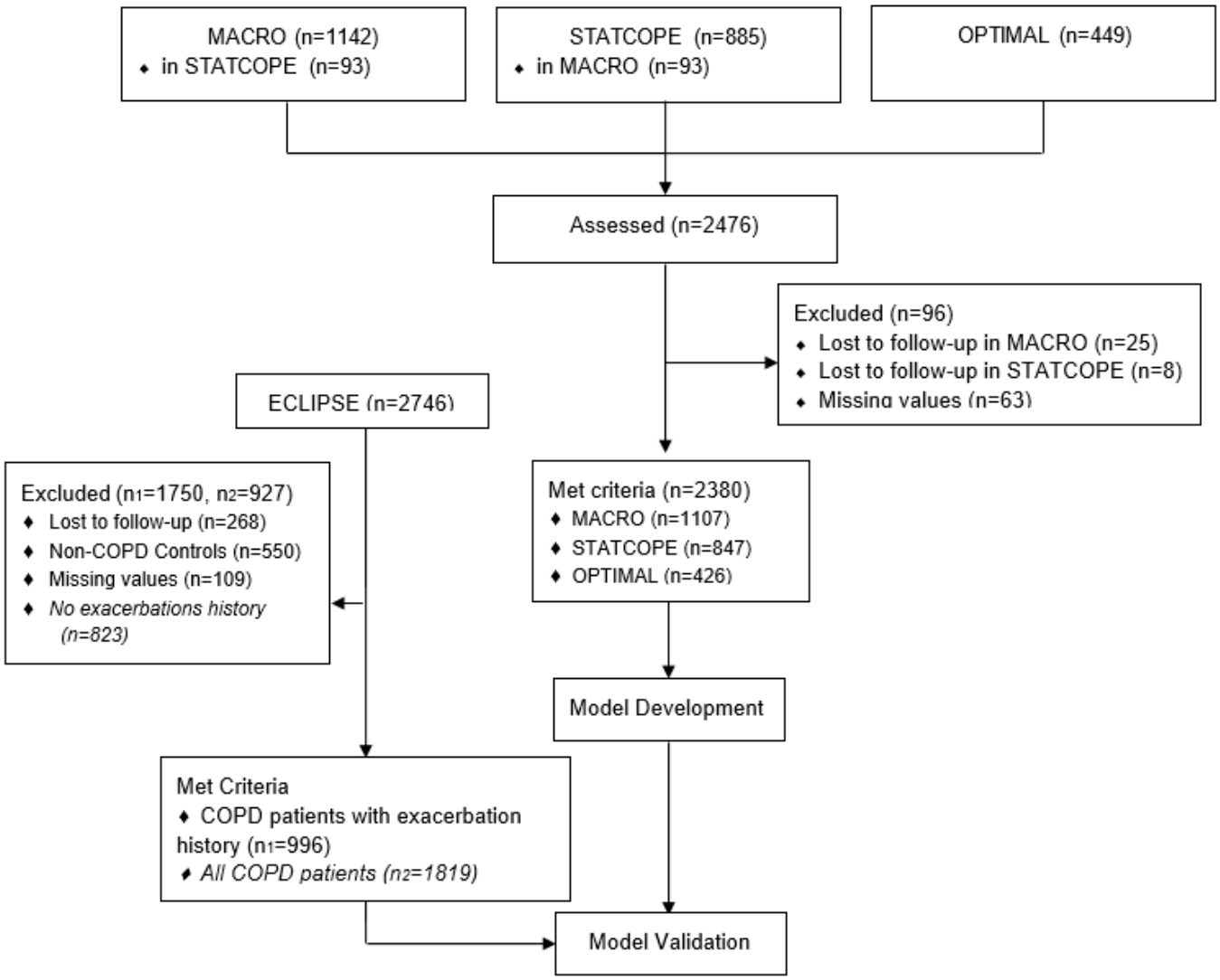
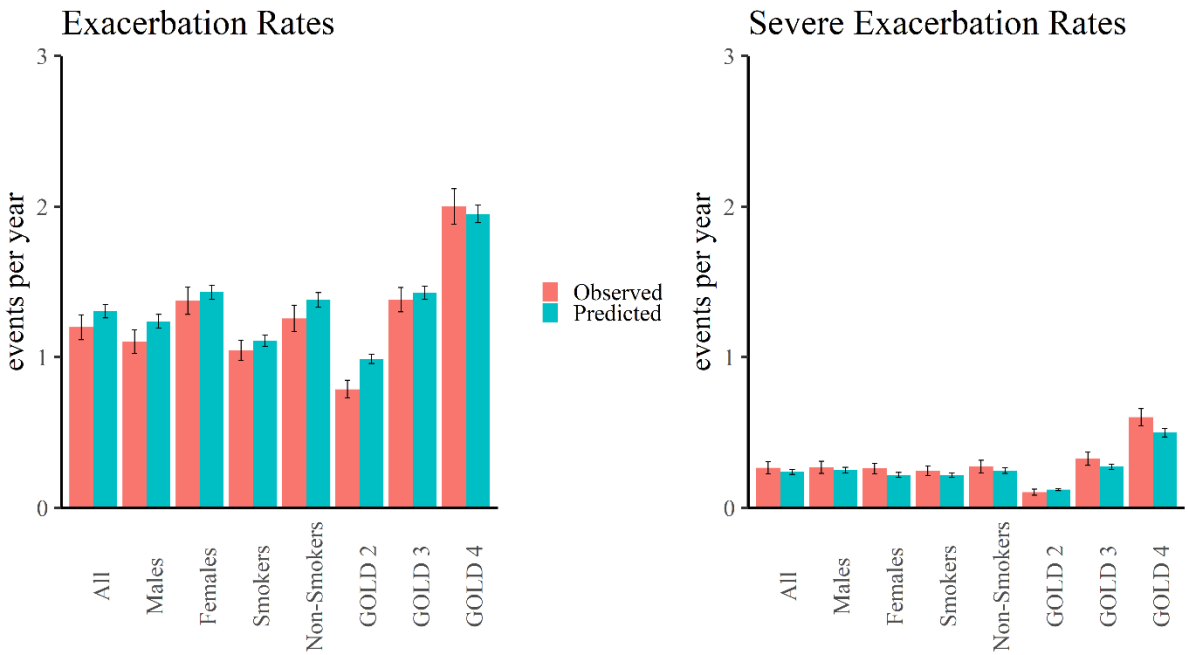


Figure 1 Flow diagram

Subgroup Calibration performance of ACCEPT

A) In all COPD patients in ECLIPSE Study



B) In COPD patients with a history of exacerbation in ECLIPSE Study

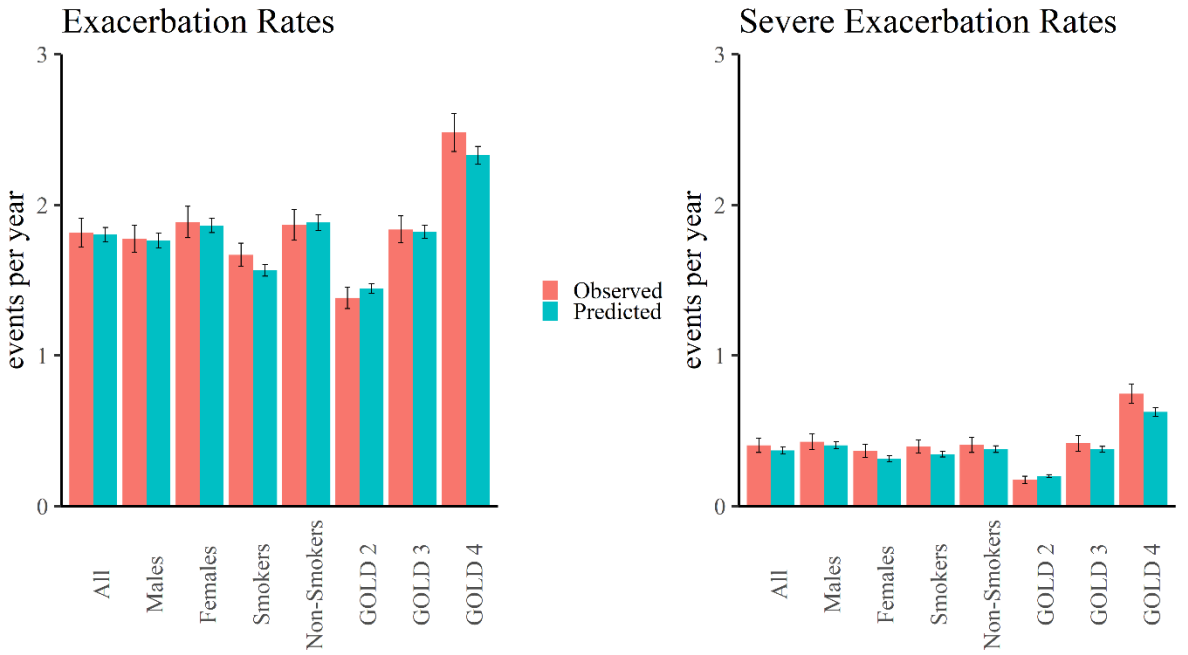
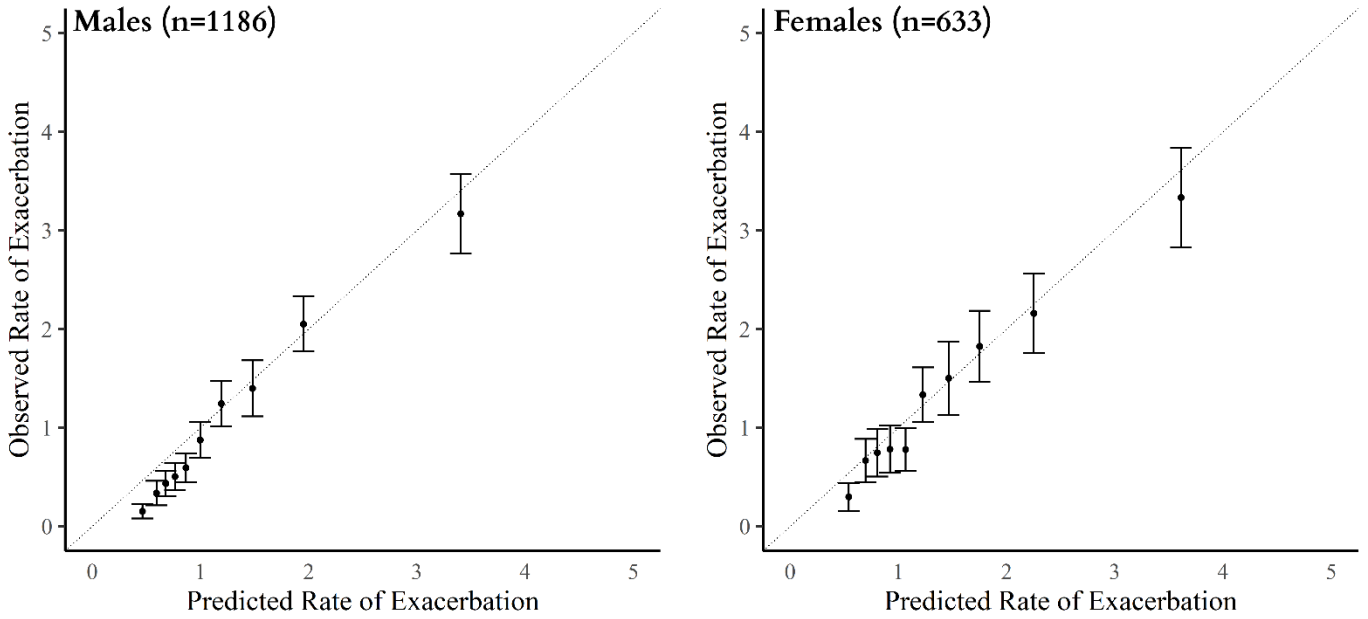


Figure 2 Calibration of exacerbation and severe exacerbation rate in subgroups of external dataset

Calibration performance of ACCEPT

A) In all COPD patients in ECLIPSE Study



B) In COPD patients with a history of exacerbation in ECLIPSE Study

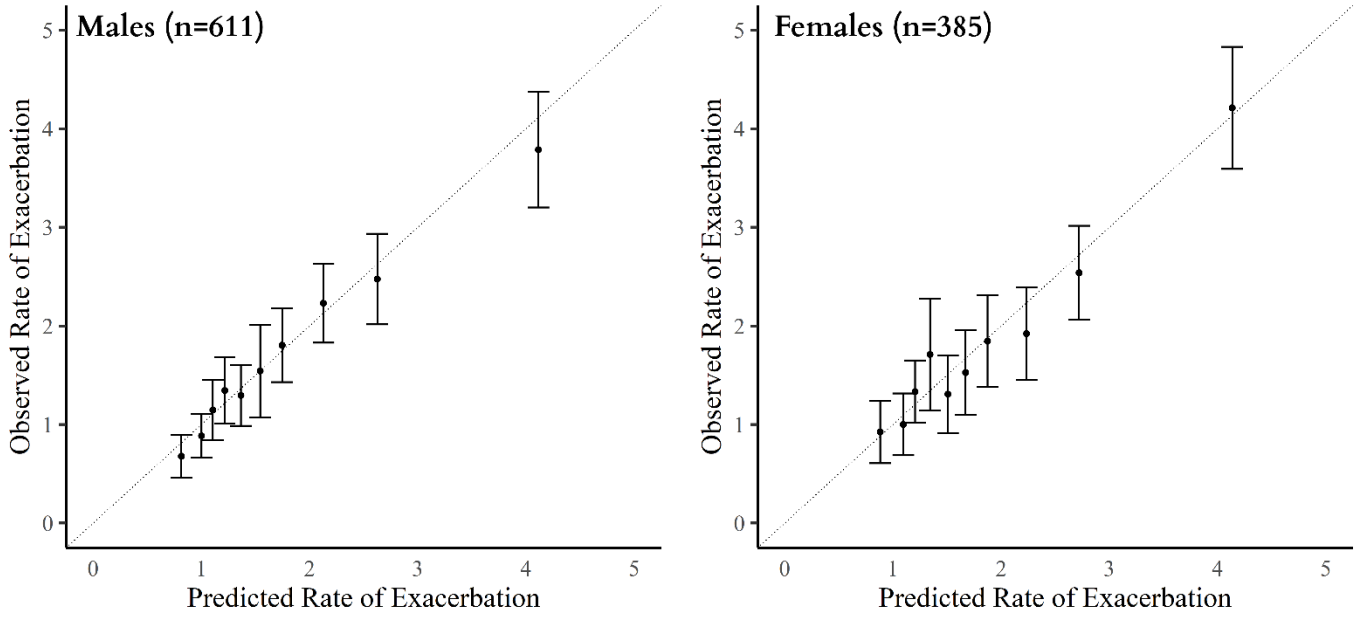
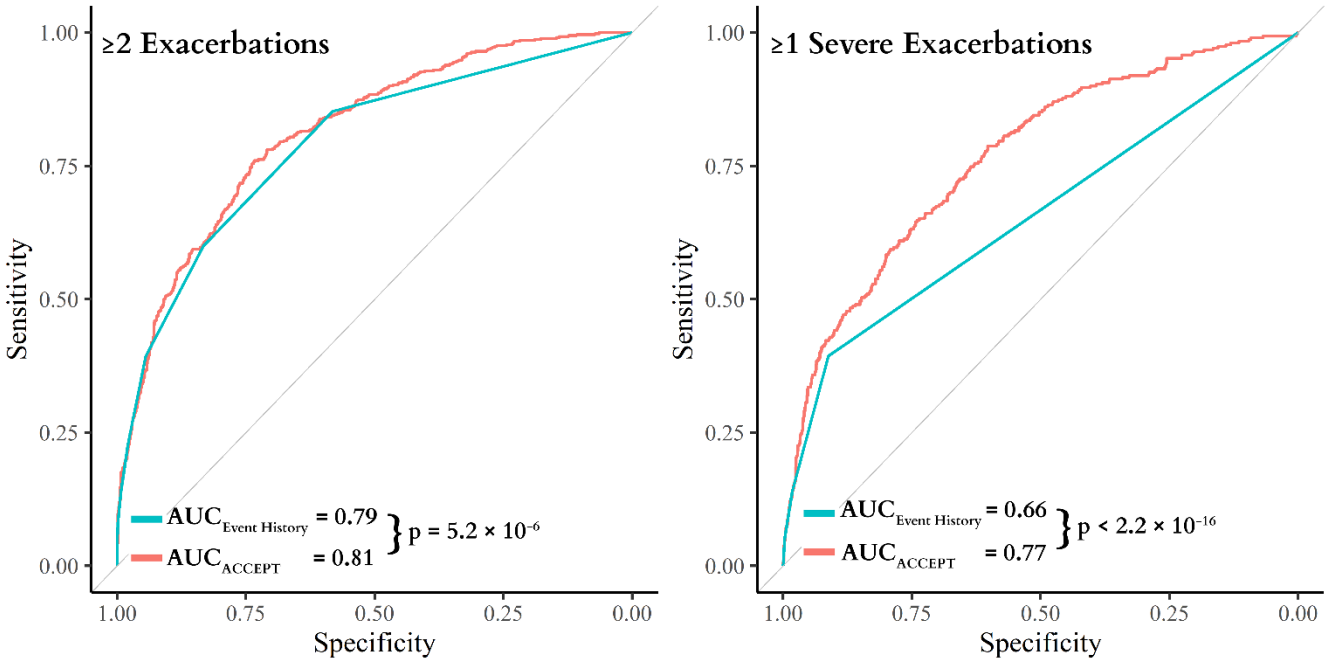


Figure 3 Calibration plot comparing per decile predicted vs. observed rate of exacerbations in female (right) and male (left) participants in the external validation dataset. Perfect agreement is shown by the dashed line.

Discrimination performance of ACCEPT vs. event history

A) In all COPD patients in ECLIPSE Study



B) In COPD patients with a history of exacerbation in ECLIPSE Study

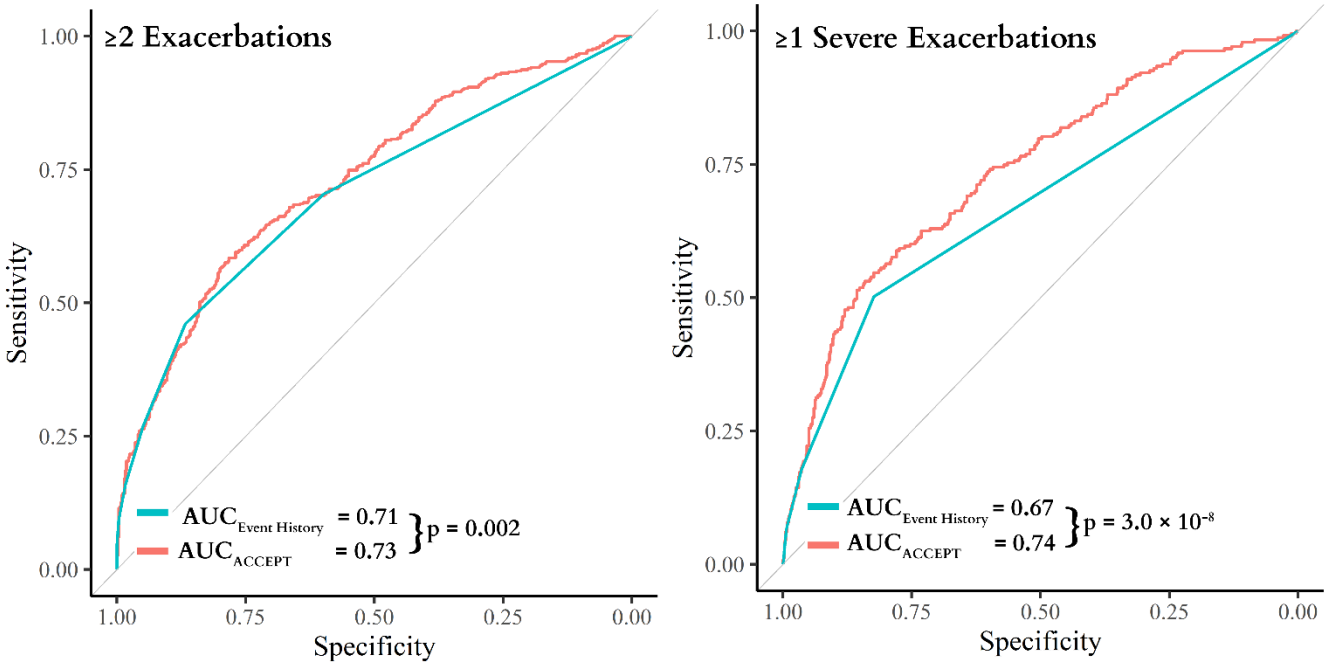


Figure 4 Receiver operating characteristic (ROC) curves showing discriminative performance of ACCEPT compared with last year's history of exacerbation among patients with a prior history of exacerbation and all patients in the external validation dataset. In line with GOLD recommendations, Area-under-the-curve (AUC) is shown for predicting at least two exacerbations and at least of severe exacerbation. DeLong's test for two correlated ROC curves was used to produce p-values.

References:

1 Aaron SD. Management and prevention of exacerbations of COPD. *BMJ* 2014; **349**: g5237.

2 Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2010; **363**: 1128–38.

3 Global Initiative for Chronic Obstructive Lung Disease. POCKET GUIDE TO COPD DIAGNOSIS, MANAGEMENT, AND PREVENTION: A Guide for Health Care Professionals. *Glob Initiat Chronic Obstr Lung Dis* 2019. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-DRAFT-v1.7-14Nov2018-WMS.pdf.

4 Obeidat M, Sadatsafavi M, Sin DD. Precision health: treating the individual patient with chronic obstructive pulmonary disease. *Med J Aust*; **0**. DOI:10.5694/mja2.50138.

5 Celli BR, Cote CG, Marin JM, *et al.* The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2004; **350**: 1005–12.

6 Guerra B, Gaveikaite V, Bianchi C, Puhan MA. Prediction models for exacerbations in patients with COPD. *Eur Respir Rev* 2017; **26**: 160061.

7 Collins GS, Reitsma JB, Altman DG, Moons K. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. *BMC Med* 2015; **13**: 1.

8 Albert RK, Connett J, Bailey WC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; **365**: 689–98.

9 Criner GJ, Connett JE, Aaron SD, *et al.* Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD. *N Engl J Med* 2014; **370**: 2201–10.

10 Aaron SD, Vandemheen KL, Fergusson D, *et al.* Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease: A Randomized Trial. *Ann Intern Med* 2007; **146**: 545.

11 Agusti A, Calverley PM, Celli B, *et al.* Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; **11**: 122.

12 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; **159**: 179–87.

13 Morishita-Katsu M, Nishimura K, Taniguchi H, *et al.* The COPD assessment test and St George's Respiratory Questionnaire: are they equivalent in subjects with COPD? *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 1543–51.

14 Sadatsafavi M, Sin DD, Zafari Z, *et al.* The Association Between Rate and Severity of Exacerbations in Chronic Obstructive Pulmonary Disease: An Application of a Joint Frailty-Logistic Model. *Am J Epidemiol* 2016; **184**: 681–9.

15 Ewout Steyerberg. Clinical Prediction Models - A Practical Approach to Development, Validation, and Updating. Springer New York, 2009.

16 Steyerberg EW, Vickers AJ, Cook NR, *et al.* Assessing the Performance of Prediction Models: A Framework for Traditional and Novel Measures. *Epidemiology* 2010; **21**: 128–38.

17 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44**: 837–45.

18 Almagro P, Soriano JB, Cabrera FJ, *et al.* Short- and Medium-term Prognosis in Patients Hospitalized for COPD Exacerbation: The CODEX Index. *Chest* 2014; **145**: 972–80.

19 Bertens L, Reitsma, Moons, *et al.* Development and validation of a model to predict the risk of exacerbations in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2013; : 493.

20 Kerkhof M, Freeman D, Jones R, Chisholm A, Price D. Predicting frequent COPD exacerbations using primary care data. *Int J Chron Obstruct Pulmon Dis* 2015; : 2439.

21 Annavarapu S, Goldfarb S, Gelb M, Moretz C, Renda A, Kaila S. Development and validation of a predictive model to identify patients at risk of severe COPD exacerbations using administrative claims data. *Int J Chron Obstruct Pulmon Dis* 2018; **Volume 13**: 2121–30.

22 FitzGerald JM, Sadatsafavi M. Improving precision in the prediction of asthma exacerbations. *Lancet Respir Med* 2017; **5**: 539–40.

23 Fuhlbrigge AL, Bengtsson T, Peterson S, *et al.* A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. *Lancet Respir Med* 2017; **5**: 577–90.

24 Yu T, Fain K, Boyd CM, *et al.* Benefits and harms of roflumilast in moderate to severe COPD. *Thorax* 2014; **69**: 616–22.

25 Moons KGM, Kengne AP, Grobbee DE, *et al.* Risk prediction models: II. External validation, model updating, and impact assessment. *Heart Br Card Soc* 2012; **98**: 691–8.