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

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Abstract

Background: Clinical risk prediction tools are major enablers of precision medicine. However, the majority of COPD exacerbation prediction tools do not fulfil the requirements to enable personalised COPD care. Our objective was to develop and validate an accessible tool to predict the individualised rate and severity of COPD exacerbations.

Methods: We pooled data from three COPD trials and derived a mixed-effect model to predict the rate and severity of exacerbations over a one year period. Severe exacerbations were defined as those requiring inpatient care. Clinical predictors included the history of exacerbations, age, gender, body mass index, smoking status, domiciliary oxygen therapy, lung function, symptom burden, and current medication use. An independent multicentre cohort was used to externally validate this model.

Results: The development dataset included 2,380 patients (average age 64·7, 57·7% men, average exacerbations rate 1·42/year, 20·5% severe). The validation dataset included 997 patients (average age 63·6, 61·2% men, average exacerbation rate 1·82/year, 22·0% severe). In external validation, average predicted annual exacerbation rates matched observed rates well in all patients (observed: 1·82, predicted: 1·80), females (observed: 1·88, predicted: 1·86), and males (observed: 1·77, predicted: 1·76). Area-under-curve was 0·70 (95% CI 0·66–0·73) for all exacerbations and 0·74 (95% CI 0·70–0·78) for severe exacerbations. The model is available as a web application at http://resp.core.ubc.ca/ipress/accept.

Interpretation: ACCEPT can be used as a decision tool to personalize the treatment of COPD patients with a focus on exacerbation prevention.

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1. Background and Objectives

Chronic Obstructive Pulmonary Disease (COPD) is a common and generally progressive chronic disease of the airways. It 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 COPD 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 clinics for COPD patients. This is unlike COPD-related mortality for which clinical scoring schemes such as the BODE index have been developed.[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 has the following important features: 1) it predicts both the frequency (rate) of exacerbations and their severity, two important components of the exacerbation burden; 2) it incorporates individual variability beyond model predictors, thus enabling individualised prediction; and 3) it is clinically applicable and easily accessible at point-of-care. As a decision tool, ACCEPT provides a personalised risk profile that allows clinicians to better tailor a treatment regimen to the individual patient.

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

The target population for our predictive model (ACCEPT) was COPD patients who had experienced at least one exacerbation within the preceding 12 months and were not diagnosed with asthma.

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-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 3-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 in the present study were the rates of all exacerbations and severe exacerbations alone over one year. Severe exacerbations were defined as exacerbations requiring an emergency department visit or hospitalisation. Non-severe exacerbations were defined as periods of sustained worsening of symptoms requiring a change in regular medications, typically the institution of systemic corticosteroids and/or antibiotics.[8–10]

Predictors

Predictors were chosen *a priori* based on clinical relevance and availability of predictor in all datasets. They consisted of exacerbation history over the previous year, baseline age, gender, 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. Given that such medication history is a surrogate measure of disease activity or the burden of comorbidities, their association with the outcome does not represent their causal effect. 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 as predictors for the risk prediction.

Additionally, a minimal model consisting only of age, gender, and exacerbation history was developed and tested to establish the prediction power of exacerbation history alone.

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 model development and prediction 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 the rates of exacerbations.

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.[13] In summary, this framework assigns two random-effect terms to each individual, quantifying their specific tendency towards a particular rate of exacerbations and the probability that once an exacerbation occurs, it will be severe. Through such random-effect terms, we accounted for individual heterogeneity among patients beyond predictors included in the model. 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 that will contain 95% of similar patients). Shrinkage methods were not applied given the relatively high events per predictor.[14] Despite its importance as a predictor, the history of exacerbations was not fully available in our development dataset. We, therefore, used a Bayesian approach to incorporate such history in the prediction: the distribution of random effects for a given individual was recalculated based on the number and severity of exacerbations in the previous year (details in Supplementary Material –

Appendix III). The availability of full exacerbation history in the external validation cohort enabled evaluating the validity of this approach.

External validation

To make ECLIPSE align with the target population, we only included ECLIPSE patients who had had at least one exacerbation in the first year of follow-up. 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 examined both model calibration (the degree by which predicted and actual rates are aligned) and model discrimination (the extent to which the model can separate individuals with different risks).[15] Model calibration was assessed through comparing the predicted and observed exacerbation rates among identifiable subgroups and through drawing a calibration plot, while model discrimination was evaluated by drawing the receiver operating characteristic (ROC) curve and calculating the area-under-the-curve (AUC). ROC analysis is typically based on binary outcomes. As such, for ROC and AUC calculations were based on whether any exacerbation occurred during follow-up.

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. Pooled data from the three trials generated a sample of 2,476 patients for the development dataset. We excluded 104 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 64.68, 57.69% male). Patients experienced a total of 3,056 exacerbations, 628 of which were severe. The external validation dataset, ECLIPSE, included 2,746 patients. Patients with less than 2 years of follow-up (n=23), missing values (n=200), or no previous history of exacerbations (n=1,526) were excluded, resulting in 997 patients in the external validation dataset (mean age 63.53, 61.28% 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 Material - 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 3 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 had missing data (n=63). The distribution of missing values is shown in ***Supplementary Material - Table S2.***

Model specification and performance

Table 3 provides coefficient estimates for predictors. Regression coefficients are shown as log-hazard ratios (ln-HR) to facilitate reproduction of model results and discourage causal interpretation of predictor estimates.

<<Table 3>>

Overall calibration (i.e. calibration-in-the-large) was robust in the validation dataset: predicted annual exacerbation rate closely matching the observed rate for all exacerbations (observed 1·82 events/year, predicted 1·80 events/year) and severe exacerbations (observed 0·40 events/year, predicted 0·37 events/year). A comparison of observed and predicted rates of exacerbations among commonly-reported subgroups defined by gender and smoking status in the validation dataset showed close agreement (***Table 4***, similar results for the development dataset are provided in ***Supplementary Material – Table S4).*** Calibration plots comparing per decile average rate of exacerbations showed good agreement between observed and predicted rates for both female and male patients (***Figure 2***).

Figure 3 demonstrates the ROC curves for the development and validation datasets for overall and severe exacerbations. When used to determine whether or not a patient will have at least one exacerbation, the AUC was 0·70 (95% CI 0·68–0·72) for all exacerbations and 0·74 (95% CI 0·72–0·77) for severe exacerbations in internal validation. The model retained most of its discriminative power in external validation, with the corresponding AUCs of 0·70 (95% CI 0·66–0·73) for all exacerbations and 0·74 (95% CI 0·70–0·78) for severe exacerbations. In comparison, the minimal model consisting only of

age, gender, and exacerbation history had an AUC of 0·67 (95% CI 0·64–0·70) for all exacerbation and 0·70 (95% CI 0·66–0·74) for severe exacerbation.

<<Figure 2, Figure 3, and Table 4>>

To showcase the usability of ACCEPT and facilitate its clinical implementation, we have developed and deployed an easy-to-use web application (available at http://ipress.resp.core.ubc.ca/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.

4. Discussion

While preventing exacerbations is a major goal in COPD care, no good tools to date accurately predict the rate of exacerbations in a given individual. Prior studies suggest that on average, patients with a prior history of an exacerbation are more likely to exacerbate in the future than those without such a history. 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, rather than a replacement for, this variable. 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 2 of the 27 reviewed models – CODEX[16] and Bertens' model[17] – reported on any external validation. When the availability of predictors and practical applicability were taken into account in addition to the external validation, 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[18] and Annavarapu[19] – 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, all other externally validated exacerbation models used geographically limited datasets: CODEX was Spanish[16], Bertens' model was Dutch[17], Kerkhof's model was British[18], and Annavarapu's model was based on cross-sectional data from an administrative dataset in the non-single-payer context of the United States.[19]

ACCEPT predicts the rate and severity of exacerbations jointly, as opposed to the commonly reported binary outcome of other exacerbation prediction modes. 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 clinical prediction models, as they only predict the probability of having at least one exacerbation in a single time window.[6]

ACCEPT provides reasonable discrimination (AUC 0·70 for all and 0.74 for severe exacerbations) 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.

Example of Application in Clinic

ACCEPT can combine predicted risk with effect estimates from randomized trials. This enables clinicians to personalise the treatment of COPD patients based on their individualised risk profiles. For example, a harm-benefit analysis for roflumilast 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.[20] 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, given that 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, facilitating shared decision making between the patient and the care provider.

As a case study, consider a 70-year-old female COPD patient with chronic bronchitis phenotype, who is currently a smoker, has an FEV1 of 40%, a BMI of 25, and a history of 3 exacerbations in the past 12 months, two of which required emergency room visit. The patient has not received domiciliary oxygen therapy within the past year, and is currently on LAMAs, LABAs, and inhaled corticosteroids, but not statins. SGRQ was not available in the clinic, but the patient had a COPD Assessment Test (CAT) score of 15. For this patient, the web app will predict an exacerbation risk of 88.8%, a severe exacerbation risk of 38.7%, an exacerbation rate of 2.8 events per year, and a severe exacerbation rate of 1 event per year. ***Figure 4*** illustrates the calculated azithromycin treatment effects for this patient. As shown in the web application, the model predicts that azithromycin (250mg/day) reduces the relative hazard of exacerbation by approximately 25%, in this case from 2.8 exacerbations/year to 2.1 exacerbations/year. Clinicians and their patients can weigh the predicted benefit against potential side effects and patient-specific risk thresholds to make a shared decision on whether to initiate azithromycin treatment. When a harm-benefit analysis is available, as is the case for roflumilast[20], the app goes one step further and provides the probability of a net benefit. For this particular patient, the probability of roflumilast (500 µg/day) providing a net benefit is estimated to be between 90% and 100%.

Further, this framework can potentially be used for prognostic enrichment of randomized trials by identifying patients who are more likely to experience COPD exacerbations in the future. 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.[21,22]

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. Importantly, 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 might be necessary to adapt ACCEPT to other geographical locations and contexts.[23]

Compared to simple scoring systems such as the BODE index that can be manually calculated, ACCEPT requires relatively sophisticated computation (especially the Bayesian updating of estimates to incorporate previous history of exacerbations). 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 implementation and for research: we have provided a web application as well as a spreadsheet implementation for clinicians, and an R package for epidemiologists and statisticians.

We also emphasize 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 exacerbate, but is not causally interpretable.

How to Access the Model

ACCEPT is open-source and publicly available as a web application at http://ipress.resp.core.ubc.ca/accept.

Additionally, we provide an open-source R package, a spreadsheet template, public application programming interfaces (APIs) through the PRISM platform, the SAS code for fitting the model, as well as R codes used for post-hoc analysis and plots through the ACCEPT homepage accessible 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 future rate and severity of exacerbations and provides individualised estimates of risks and uncertainty in predictions. ACCEPT showed robust calibration in the external validation data, and had reasonable discriminatory power in predicting the rate and severity of COPD exacerbations 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 objectively project the risk and response to treatments to enable shared, informed decision making between patients and care providers, facilitating precision medicine in COPD.

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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.

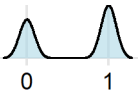
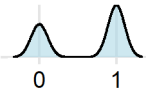
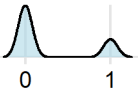
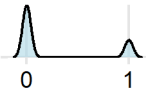
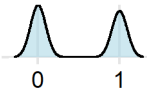
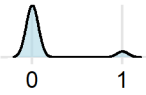
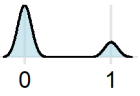
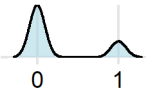
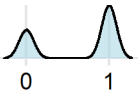
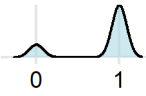
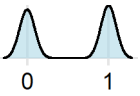
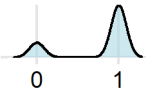
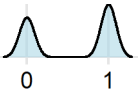
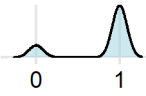
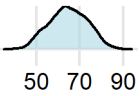
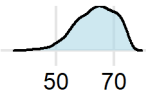
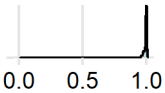
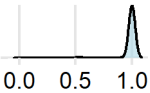
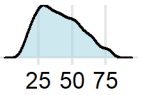
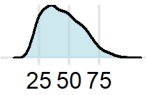
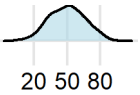
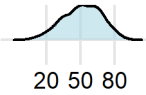
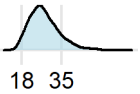
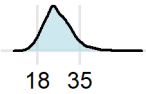
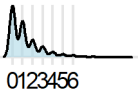
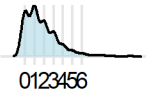
Declaration of Interest

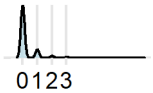
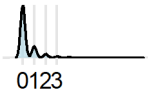
Authors declare no conflicts of interest.

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

Data Source	Design	Intervention	N (follow–up years)	# of exacerbations total (severe)	Study Period (Follow-up)	Centres	Inclusion Criteria	Exclusion Criteria
Development								
MACRO	Randomized trial	Azithromycin	1142 (1051)	1285 (356)	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	885 (1537)	1537 (445)	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	449 (404)	520 (116)	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.
		Total	2476 (2992)	3342 (917)				
Validation								
ECLIPSE	Cohort		2746 (~6000)	6349 (1411)	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.

Table 2 Comparison of Development and Validation Datasets

Predictor	Development (n = 2380)		Validation - ECLISPE Study (n=997)	
	%	*Distribution*	*%*	*Distribution*
Male Gender	57·69		61·28	
Current Smokers	25·80		25·48	
O_2 therapy previous year	46·85		10·23	
On statins	22·65		23·07	
On LAMA	65·04		80·54	
On LABA	52·06		78·54	
On ICS	57·23		81·34	
	Mean (SD)	*Distribution*	*Mean (SD)*	*Distribution*
Age, years	64·68 (8·75)		63·53 (6·90)	
Follow–up time, years	0·90 (0·23)		0·97 (0·13)	
FEV_1, % predicted	40·60 (15·93)		44·60 (15·88)	
SGRQ Score [b]	49·95 (16·72)		51·43 (17·03)	
BMI	27·53 (6·44)		26·21 (5·77)	
Rate of Exacerbations [c]	Rate	Distribution	Rate	
Total	1·42		1·82	

Severe/very severe	0·29		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 Log-hazard of model coefficients for the Joint Rate–Severity Prediction Model of COPD Exacerbations [a]

Predictor	Rate Component			Severity Component		
	Estimate	95% CI	p	Estimate	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]; HR, hazard ratio; OR, odds ratio; 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 External Validation: Observed and predicted annual rate of exacerbations amongst different subgroups of the external validation dataset

Data set	Subgroup	Annual Rate of all exacerbations		Annual Rate of severe Exacerbations	
		Observed	Predicted	Observed	Predicted
Validation (ECLIPSE)	All	1·82	1·80	0·40	0·37
	Males	1·77	1·76	0·43	0·41
	Female	1·88	1·86	0·37	0·31
	Smokers	1·66	1·56	0·40	0·34
	Non-Smokers	1·87	1·88	0·41	0·38
	Male Smokers	1·59	1·50	0·47	0·37
	Male Non-smokers	1·83	1·84	0·42	0·42
	Females Smokers	1·75	1·64	0·30	0·31
	Female Non-smokers	1·93	1·95	0·39	0·32

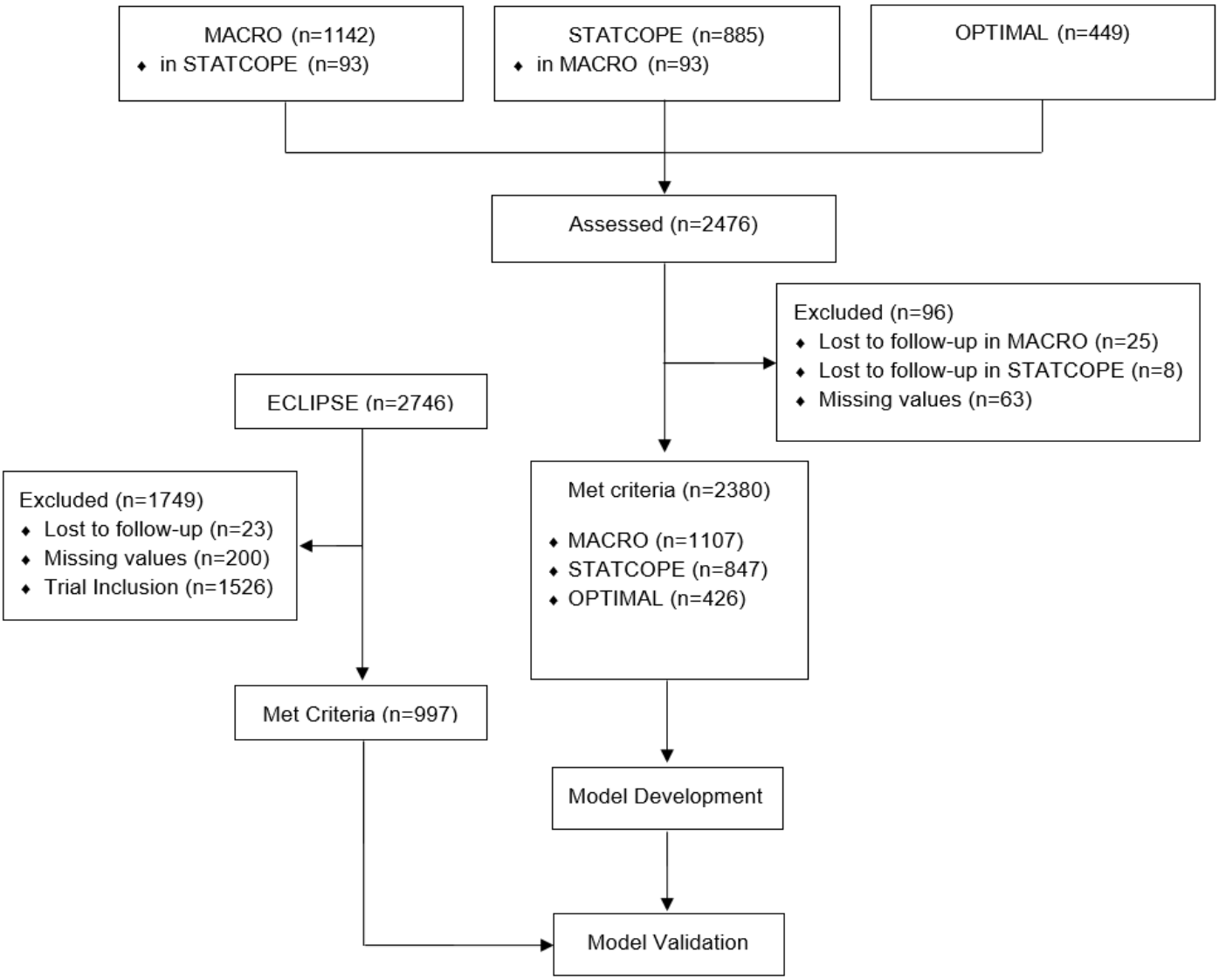


Figure 1 Flow diagram

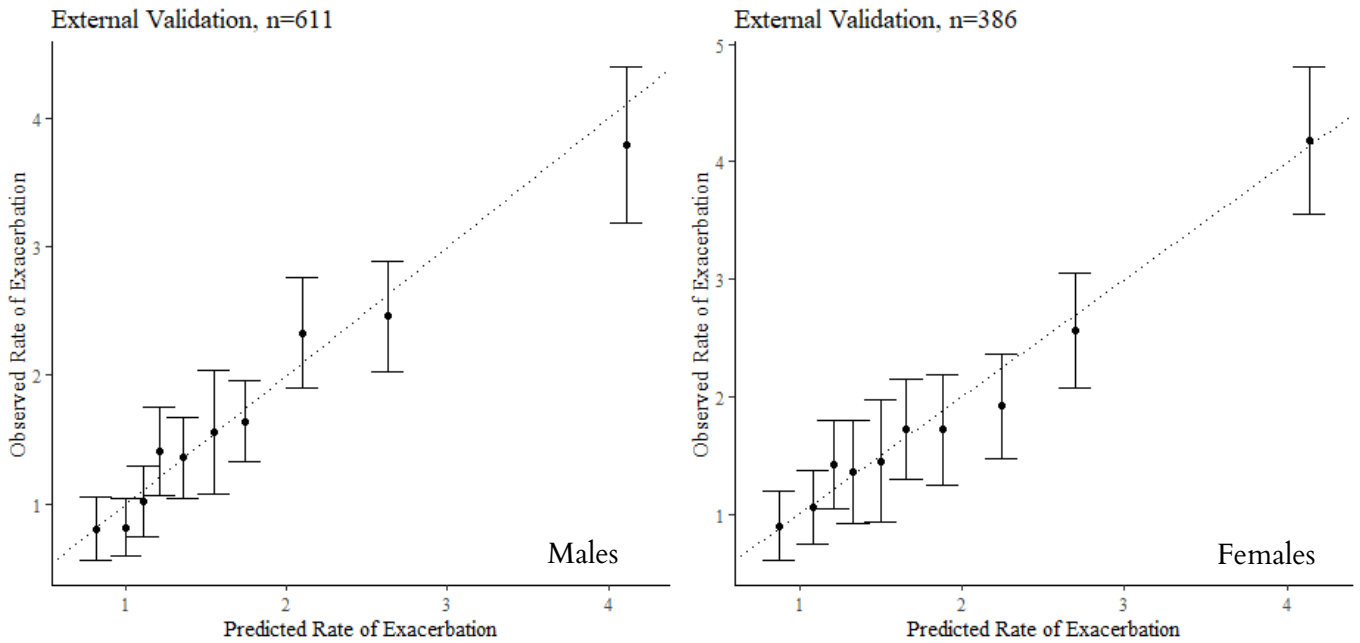


Figure 2 Calibration plot comparing per decile predicted vs. observed rate of exacerbations in female (right) and male (left) participants in the external validation dataset. Perfect agreement is shown by the dashed line.

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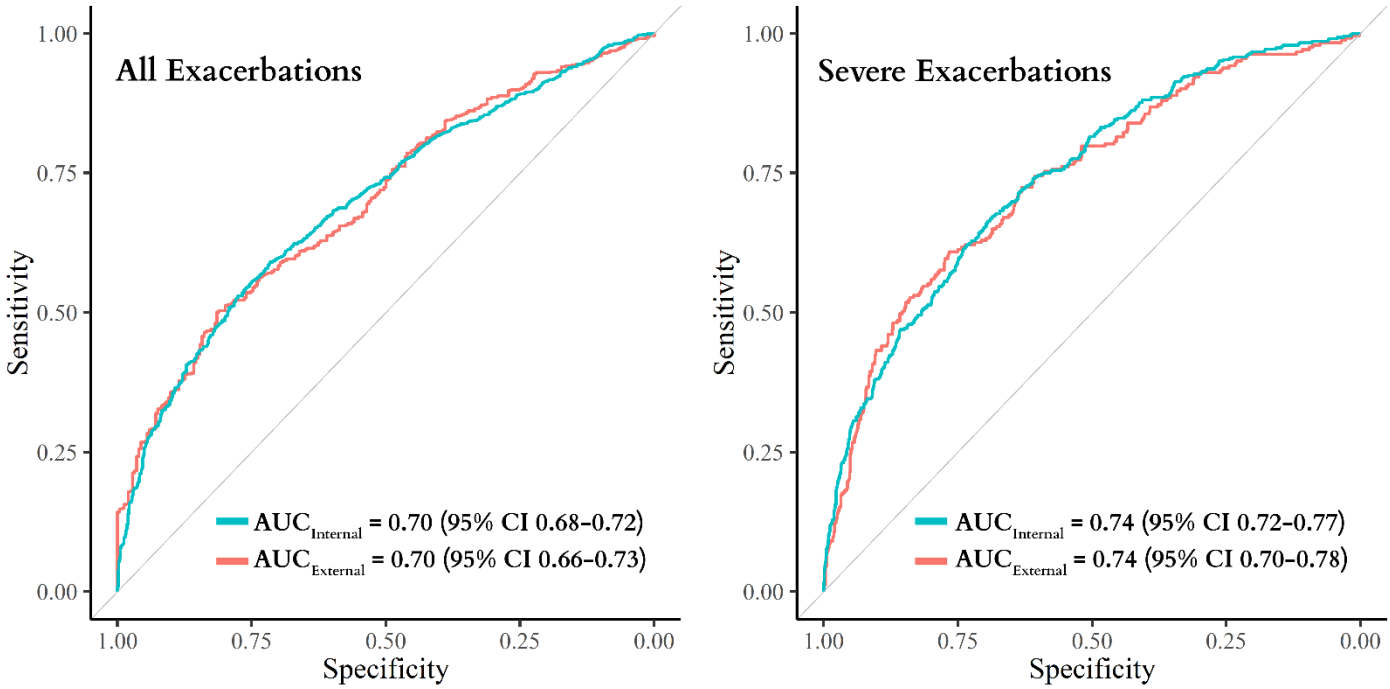
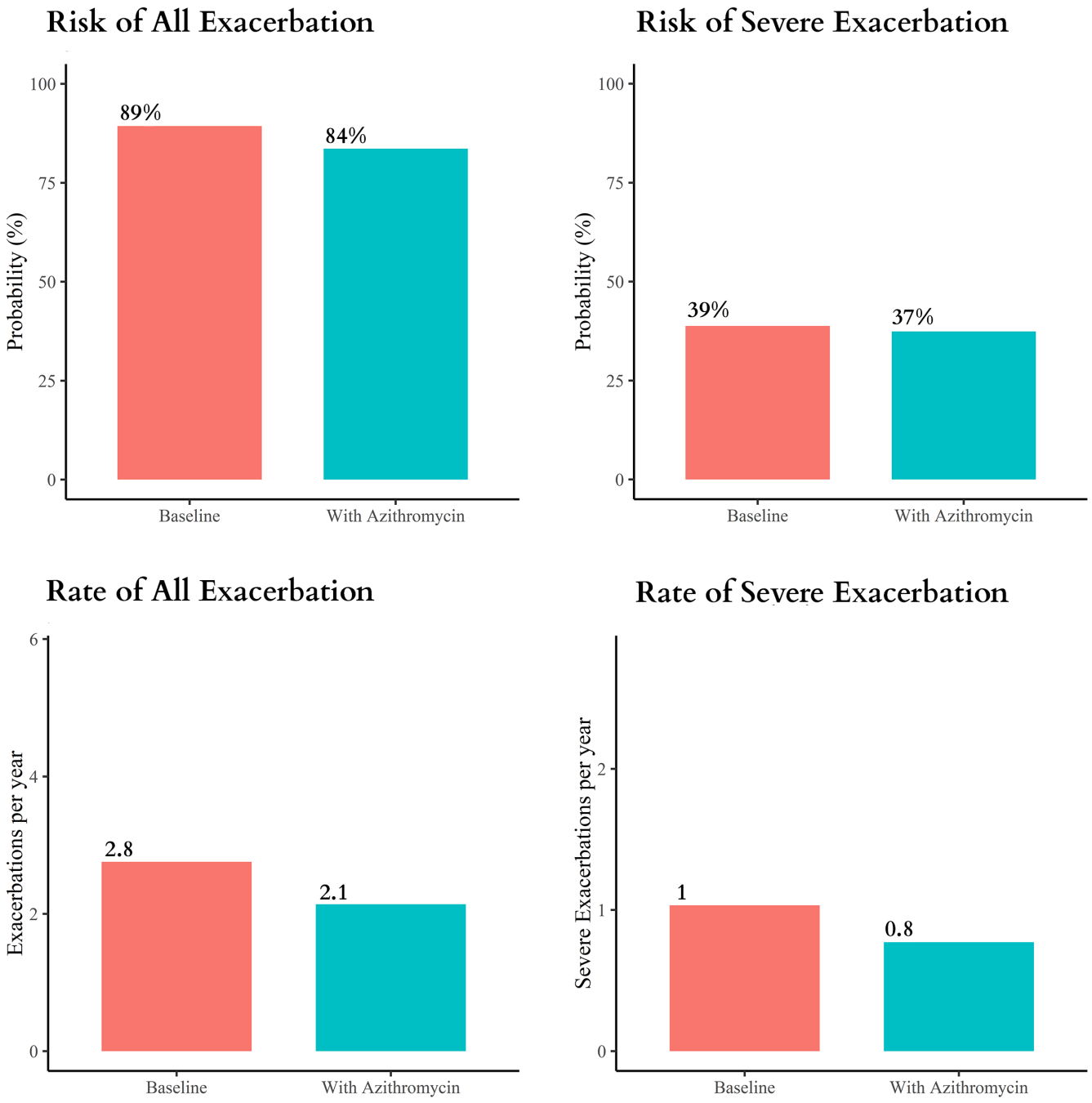


Figure 3 Receiver operating characteristic (ROC) curves for predicting whether the patient will have an exacerbation within the next year. Area-under-the-curve (AUC) and 95% confidence intervals (in brackets) are shown for the internal and external validation.

Case Study



ACCEPT model predictions for a 70 years old smoker female with an FEV1 of 40%, a BMI of 25, and a history of 3 exacerbations within the past 12 months two of which required emergency room visit. The patient was on LAMAs, LABAs, and inhaled corticosteroids. SGRQ score was not available. CAT score was 15. The patient was not receiving domiciliary oxygen therapy.

Figure 4

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