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. A recent systematic review reported that 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 individualized 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. Clinical predictors were history of exacerbations, age, gender, smoking status, domiciliary oxygen therapy, baseline forced expiratory volume at one second, St. George Respiratory Questionnaire scores, body mass index, and current medications profile. 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 annual rate of exacerbations 1·42, 20.5% severe, requiring inpatient care). Validation dataset included 997 patients (average age 63·53, 61·23% men, average annual rate of exacerbation 1·82, 22.0% severe). In external validation, average predicted annual exacerbation rates matched observed rates well in all (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 0·69 (95% CI 0·66–0·73) for all exacerbations and 0·72 (95% CI 0·68–0·76) 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 for 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. Although the use of this historical variable improves the risk-benefit ratio of therapeutic interventions, there remains significant amount of heterogeneity within each subgroup of patients.[3]

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 simple clinical scoring schemes such as the BODE index have had some success.[4] A 2017 systematic review by Guerra and colleagues identified 27 prediction tools for COPD exacerbations.[5] Among these, only two reported on the validation of the model and none were deemed ready for personalized COPD management in the clinic.[5]

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 individualized 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.[6]

Source of data and target population

We pooled data across all arms of three randomized controlled trials: MACRO[7], STATCOPE[8], and OPTIMAL[9] to create the development dataset. We used ECLIPSE[10] – an independent longitudinal cohort – for external validation.

The details of each of these studies have been previously published. Briefly, the MACRO trial[7] evaluated the effect of daily low-dose azithromycin therapy on the rate of exacerbations in COPD patients, the STATCOPE trial evaluated the effects of daily simvastatin therapy on the rates of exacerbation[8] and the OPTIMAL trial evaluated the effects of tiotropium-salmeterol on rates of exacerbation compared with tiotropium-fluticasone and tiotropium-placebo.[9] ECLIPSE was a 3-year observational study that characterised COPD phenotypes and identified markers of disease progression.[10] In all 3 trials, which comprised the development dataset, study patients reported a history of at least 1 moderate to severe exacerbations over the previous 12 months. ***Table 1*** provides a more detailed summary of these studies.

Outcomes

The outcomes of interest in the present study were the rates of all exacerbations and severe exacerbations alone over one year. Moderate 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.[7–9] Severe exacerbations were defined as exacerbations requiring emergency department visit or hospitalisation.

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

Predictors

Predictors were chosen *a priori* based on clinical relevance and availability of predictor in all datasets. Predictors included in the model were exacerbation history over the previous year, baseline age, gender, smoking status, use of domiciliary oxygen therapy, post-bronchodilator forced expiratory volume in one second (Hankinson's FEV_1 % predicted[11]), 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. Among the treatments to which patients were randomized to during the

trials (azithromycin in MACRO, statins in STATCOPE, LABA, LAMA, and ICS in OPTIMAL), only azithromycin showed a statistically significant effect on exacerbations and was included in the prediction tool to model the individual-specific benefit of maintenance azithromycin therapy for each patient.

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 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 both the rate and severity of exacerbations. We have previously published the details of this approach elsewhere.[12] 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. This framework fully specifies, for each patient, the hazard of moderate and severe exacerbations at any given point during follow-up and quantifies the degree of uncertainty. In particular, two forms of uncertainty in predictions are 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). We accounted for individual heterogeneity among patients beyond predictors included in the model (i.e. genetics, comorbidities, nutrition, environmental exposures, etc.) by letting the intercept of the regression model vary across individuals.

We tested exponential, Weibull, log-logistics, and log-normal distributions for the survival function and assessed the internal validity of the resulting models by comparing observed and predicted cumulative number of exacerbations, as well as goodness-of-fit measures of Akaike information criterion (AIC) and Bayesian information criterion (BIC).

Despite its importance as a predictor, history of exacerbations was not available in our development dataset. We therefore used a Bayesian approach to determine the expected number of all and severe

exacerbations for each patient. The distribution of possible random effects for a given individual was recalculated based on the number of exacerbations within the previous year. Shrinkage methods were not applied given the relatively high events per predictor.[13] No model updating (i.e. recalibration) was performed.

We refer the interested reader to the published SAS code for more information on the technical details of the model.

External validation

In the ECLIPSE study, we used exacerbation data from the second year of follow-up for model validation and the exacerbation data from first year as a proxy for "prior history of exacerbation". To make ECLIPSE align with the development dataset and the target population of the model, we only included ECLIPSE patients who had had at least one exacerbation in the first year of follow-up.

Ethics Approval

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

3. Results

Participants

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). Patients experienced a total of 3,056 exacerbations (1,597 from MACRO, 850 from STATCOPE Study, and 609 from OPTIMAL), 628 of which were severe (347 in MACRO, 168 in STATCOPE and 113 in OPTIMAL).

The external validation dataset ECLIPSE, included 2,746 patients. ***Table 2*** provides a detailed comparison of the development and validation datasets, including comparisons of the demographic, predictor, and outcomes. Patients with follow-up of less than 2 years (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.

Table S1 shows the distribution of baseline predictors in the development dataset. Most predictors had similar distributions among the 3 trials with a few exceptions: (1) none of STATCOPE participants had a

history of statin use because patients with cardiovascular co-morbidities were excluded from this trial; (2) a smaller proportion of OPTIMAL patients used oxygen therapy or LABAs than in STATCOPE; and (3) the proportion of patients on ICS was lower in the STATCOPE trial.

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. Subjects with missing predictors who were excluded from the analysis (n=63). The distribution of missing values is shown in ***Table S2.***

Model development and specifications

Seasonality did not improve goodness-of-fit statistics and was removed because of significant increase in computational processing time which would hinder clinical implementation.

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 inference from predictor estimates.

Model performance

Overall calibration was robust in the validation dataset: predicted annual exacerbation rate for all patients was 1·803 events/year, closely matching the observed rate of 1·800 (95% CI 1·798–1·801) events/year. A comparison of average rates of exacerbations among commonly-reported subgroups defined by gender and smoking status showed close agreement between the observed rates and the ones predicted by the model both in development (***Table S4)*** and external validation datasets (***Table 4***). Calibration plots comparing per decile average rate of exacerbations showed good agreement between observed and predicted rates for both female and male patients (***Figure 3***).

When used to determine whether or not a patient will have at least one exacerbation or one severe exacerbation within the next year, the receiver-operating curves (ROC) showed respective AUCs of 0·70 (95% CI 0·68–0·72) and 0·74 (95% CI 0·71–0·76) for all and severe exacerbations in internal validation. The model retained most of its discriminative power in external validation (***Figure 2)***, with the corresponding AUCs of 0·69 (95% CI 0·66–0·73) for moderate and 0·72 (95% CI 0·68–0·76) for severe exacerbations.

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 1) the probability of experiencing an exacerbation or a severe exacerbation within the next 12 months, 2) the annual rate of all and severe exacerbations, and 3) the probability of experiencing any given number of moderate and severe exacerbations.

4. Discussion

While preventing exacerbations is a major goal in COPD care, to date, there are no good tools to accurately predict the risk of exacerbation 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 past history of exacerbations is hampered by a relative poor resolution, leading to large variations in risk across and within subjects. 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[14] and Bertens' model[15] – reported any external model validation and concluded that none were ready for clinical implementation.[5] Aside from these, we are aware of only two additional prediction models – by Kerkhof[16] and Annavarapu[17] – that have reported external validation.

ACCEPT has several notable advantages over previously published COPD exacerbation models. Importantly, ACCEPT was externally validate in an independent cohort, ECLIPSE, extending its generalisability beyond therapeutic trials to the "real-world". ACCEPT is further 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[14], Bertens' model was Dutch[15], Kerkhof's model was British[16], and Annavarapu's model was based on cross-sectional data from an administrative dataset in the non-single-payer context of the United States.[17]

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 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 number of exacerbations at a given time period, time to next exacerbation, and probability of experiencing a

specific number of moderate or severe exacerbations. This is in contrast to the logistic regression models used in the majority of clinical prediction models, as they only predict probability of having at least one exacerbation at a single time point.[5]

ACCEPT provides reasonable discrimination (AUC 0·69 for all and 0.72 for severe exacerbations) and 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 slightly superior 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 both models suffered from a lack of generalisability.

In addition to predicting the risk, ACCEPT can be used to predict individualised treatment effects by combing background risk with constant effect estimates from randomized trials. This enables clinicians to personalize the treatment of COPD patients based on their individualized risk profile. For example, a harm-benefit analysis for roflumilast has shown that benefits of roflumilast outweigh potential harm when the patient has a severe exacerbation risk of at least 22%.[18]. The accompanied web app makes a recommendation for roflumilast based on whether the patient meets this threshold. Another example is preventative daily azithromycin therapy, which is associated with increased risk of hearing impairment and potential for antimicrobial resistance, and thus should be reserved for those at the highest risk of future exacerbations.[7] The accompanied web app illustrates this application by showing the risk and the rate of exacerbations with and without daily azithromycin therapy.

ACCEPT can also 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[19,20], the required sample size and consequently the cost of large trials can be substantially reduced by recruiting patients above a certain threshold of expected exacerbation rate.

ACCEPT is highly accessible and ready for clinical implementation. It builds upon a well-accepted predictor (i.e. history of exacerbation in the prior year) that is used commonly in clinical practice and in therapeutic COPD trials. Thus, ACCEPT can be used as a complement to, rather than a replacement for, this variable. Additional simplified versions of the model make it useful for scenarios where either SGRQ score or FEV1 are not available.

ACCEPT is open-source and easily accessible to a wide range of end-users: we provide a web application for clinicians, an R package for epidemiologists and statisticians, and a standardized API to enable EMR and telemedicine integration.

Limitations

Importantly, our model may not be generalisable to asthma patients, lifetime non-smokers, patients younger than 40 and older than 80, patients without a history of exacerbation within the past year, 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.[21]

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 0·83, 95% CI 0·73–0·94) is one such example. Smoking is likely a marker of disease severity with sicker patients less likely to smoke than those with milder disease.

Predictions of the model are based on predictor values at baseline only and become less accurate as time from baseline increases; predictions beyond the one-year time horizon may not be valid. The pooled trial data we used to develop the model lacked complete data on symptoms, comorbidities, vaccination, blood markers (e.g. eosinophil count), and socio-economic status. As such, these predictors could not be incorporated into the model.

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 available at and public application programming interfaces (APIs) for R and Microsoft Excel through the PRSIM model cloud platform. The SAS code for fitting the model is also publicly available through ACCEPT homepage at http://resp.core.ubc.ca/research/Specific_Projects/accept.

5. Conclusions

ACCEPT is a highly generalizable prediction model that has been externally validated and outperformed previously published exacerbation prediction models. ACCEPT shows reasonable discriminatory power in predicting the rate and severity of COPD exacerbations in individuals with a history of such

exacerbations in the past year. It can quantify the degree of uncertainty due to between-individual variability in tendency towards exacerbations. Objective prediction of outcomes given each patient's unique characteristics can help clinicians to tailor treatment of COPD patients based on their individualized prognosis. In many other disciplines, objective risk prediction has become a cornerstone of disease management. The Framingham Risk Score in Cardiology is a great example of this approach. 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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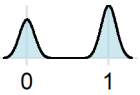
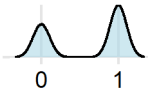
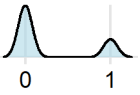
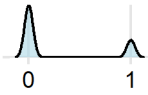
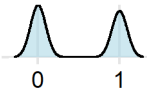
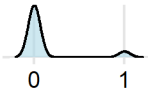
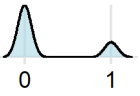
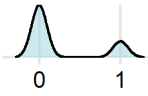
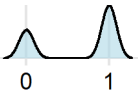
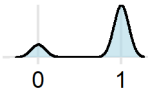
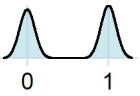
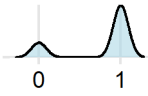
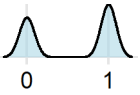
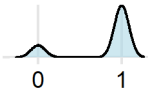
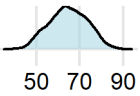
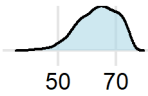
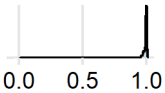
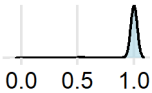
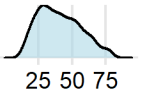
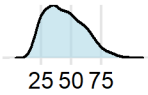
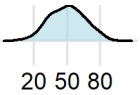
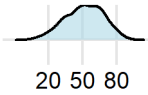
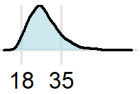
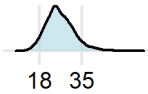
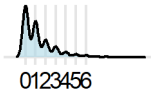
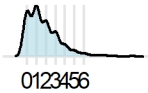
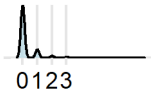
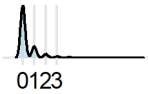
Table 1 Available datasets with data on the rate, time, and severity of COPD exacerbations.

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 last yr. Hospitalization or ER visit.	Asthma. Exacerbation in last month. HR above 100 /min. QT_C >450ms. QT_C prolonging or TdP-related medication except 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 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 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[11]; 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[11]; 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 - Exacerbations		Annual Rate - 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	0·31

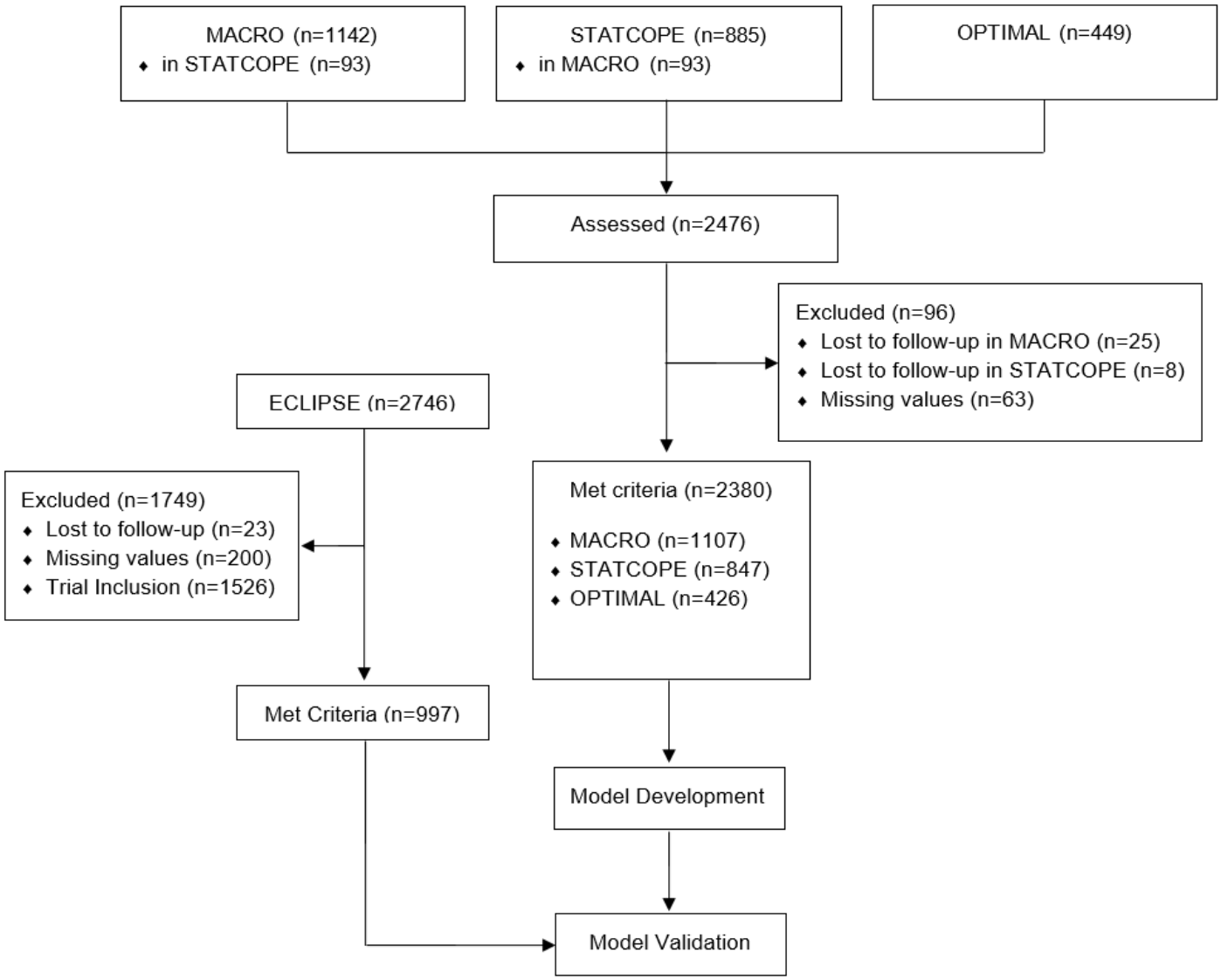


Figure 1 Flow diagram

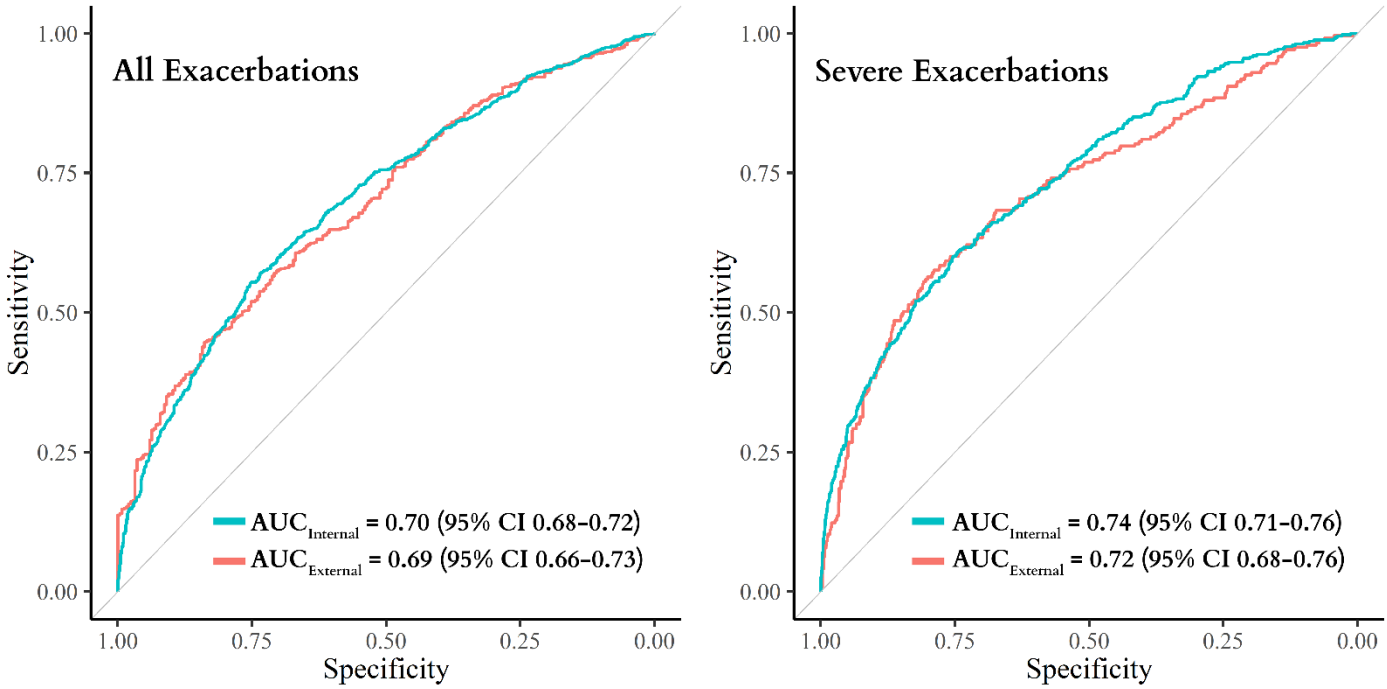


Figure 2 Receiver operating characteristic (ROC) curves for predicting whether the patient will have any exacerbation within the next year. Area-under-curve (AUCs) and 95% confidence intervals (in brackets) are shown for the internal and external validation.

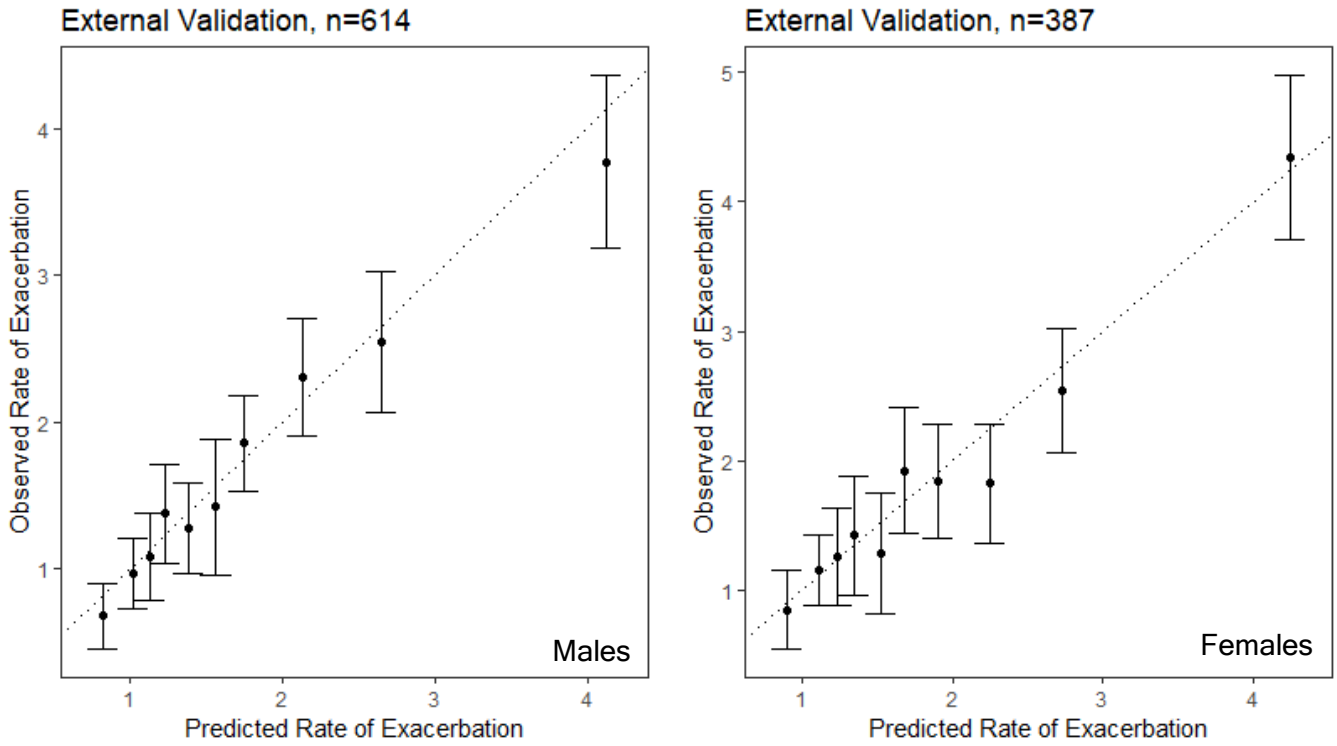


Figure 3 Calibration plot comparing per decile predicted vs. observed rate of exacerbations in female (right) and male (left) participants in the external validation dataset. Perfect agreement is shown by the dashed line.

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