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ORIGINAL RESEARCH

A Prediction Scoring Model for the Effect of Withdrawal or Addition of Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease

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Purpose: The aims of this study were to develop a scoring model that predicts the effects of withdrawing inhaled corticosteroids (ICSs) from triple therapy and to examine its adaptability when applied to assess the effect of adding ICSs to dual bronchodilators patients with chronic obstructive pulmonary disease (COPD).

Patients and Methods: A scoring model was developed using the IMPACT study dataset, consisting of 2389 COPD patients treated with triple therapy before enrollment (ICS withdrawal dataset). The developed model consisted of COPD duration, Acute exacerbation history, Sex, Pulmonary function tests, blood Eosinophil count, and Race (CASPER) and was used to predict composite events of moderate-to-severe exacerbation, all-cause mortality, and pneumonia. Treatment heterogeneity was assessed using Cox interaction analyses. The CASPER model was applied to 540 COPD patients treated with dual bronchodilator before enrollment (ICS addition dataset). Validity was assessed using Harrell's C-index, time-dependent receiver operating characteristic curves, and calibration plots.

Results: The cumulative incidence of the composite event was 60.1% over 12 months in the ICS withdrawal dataset. Cox interaction analyses revealed that ICS was different according to race and blood eosinophil counts. The hazard ratios (HRs) for dual bronchodilator compared with triple therapy were 1.318 (95% confidence interval (CI)=1.170–1.485; *P*-value <0.001) in whites and 0.922 (95% CI = 0.712–1.195; *P*-value=0.541) in other races. The treatment effect was different in the eosinophil count ≥0.3 group (HR = 1.586; 95% CI = 1.274–1.975) and in the eosinophil count = 0.1–0.3 group (HR = 1.211; 95% CI = 1.041–1.408), but it was same in the eosinophil count <0.1 (HR = 1.009; *P*-value=0.940). The CASPER model performed well with good discrimination and calibration, which were superior to the prediction based on exacerbation history and blood eosinophil count.

Conclusion: The presented CASPER model might be able to predict and compare the risk of composite events when dual bronchodilator or triple therapy is administered to COPD patients.

Keywords: chronic obstructive pulmonary disease, inhaled corticosteroid, exacerbation, mortality, pneumonia

Introduction

Chronic obstructive pulmonary disease (COPD) is among the most common causes of death in the world.[1] The mainstay of treatment for COPD is inhaled bronchodilator therapy.[2] Conversely, the role of inhaled corticosteroids (ICSs) in patients with COPD remains unclear. Some guidelines recommend the use of ICSs depending on the blood eosinophil count or history of exacerbation in the previous year, but others emphasize only the history of exacerbation, without blood eosinophil count.[2–4]

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The treatment goal in COPD is to alleviate symptoms and to reduce the frequency of exacerbation and mortality without increasing the adverse effects.[2] However, the beneficial effects in preventing exacerbation and adverse effects from additional ICSs use combined with bronchodilators were not consistently observed in patients with COPD.[5] Recently, several randomized controlled trials comparing triple therapy, which includes a long-acting β_2 agonist (LABA), a long-acting muscarinic antagonist (LAMA), and ICSs, and dual bronchodilator therapy, which includes a LABA, and a LAMA, have been performed.[6–8] These studies showed consistent results; the addition of ICSs to treatment with dual bronchodilators reduced the risk of moderate-to-severe exacerbation compared with treatment with dual bronchodilators alone. However, the risk of pneumonia related to ICSs use was increased in these studies. Among the various adverse effects of ICSs, pneumonia is considered a common adverse effect.[9,10] In clinical practice, clinicians should be cautious in adding ICSs to dual bronchodilator and withdrawing ICSs from triple therapy in patients with COPD, because the inappropriate use of ICSs could result in adverse effects without any benefits. Exacerbation history and blood eosinophil count have been recommended as criteria for the use of ICSs.[2,4] However, there is only limited data-based evidence for this recommendation. In addition, the possibility of other factors contributing to clinical benefit and harm of ICSs should be further evaluated. Therefore, a prediction model to guide the administration of inhaled therapy for patients who would benefit from the addition of ICSs to dual bronchodilator therapy or the withdrawal of ICSs from triple therapy should be developed.

In this study, we aimed to develop a prediction scoring model using the dataset from the IMPACT study.[6] To consider both benefits and adverse effects, we use the composite events, including moderate-to-severe exacerbation, all-cause mortality, and pneumonia events, as outcomes.

Materials and Methods

Study Design and Subjects

To develop the prediction scoring model for the withdrawal of ICSs from triple therapy or the addition of ICSs to dual bronchodilator therapy, we utilized the dataset from the IMPACT study. In this study, eligible patients i) were aged ≥40 years, ii) had a ratio of postbronchodilator forced expiratory volume in 1 sec (FEV_1) to forced vital capacity (FVC) of <0.7, and iii) had COPD assessment test (CAT) score of ≥10. Patients with FEV_1 that was <50% of the predicted normal value with a history of any moderate-to-severe exacerbation in the previous year or 50–80% of the predicted normal value with at least two moderate exacerbations or one severe exacerbation in the previous year were included in this study. After enrollment, patients in the triple therapy group used a once daily combination of fluticasone furoate, umeclidinium, and vilanterol (at a dose of 100, 62.5, and 25 μg, respectively). Patients in the dual bronchodilator group used umeclidinium and vilanterol (at doses of 62.5 and 25 μg, respectively).

This study subjects were further restricted to those who were using triple therapy or dual bronchodilator therapy before enrollment because the study purpose was to evaluate the withdrawal effect of ICSs from triple therapy and to evaluate the addition of ICSs to dual bronchodilator therapy. Therefore, we excluded patients who had used other inhaler regimens before enrollment. In addition, we excluded patients with a postbronchodilator ratio of FEV_1 to FVC ≥0.7 at the time of enrollment. We classified the subjects into the ICS withdrawal and ICS addition datasets. Patients in the ICS withdrawal dataset had used triple therapy before study enrollment. In this dataset, we investigated the ICS withdrawal effect in the triple therapy group compared with the dual bronchodilator group. Patients who had used dual bronchodilator without ICSs before study enrollment were included in the ICS addition dataset. In this dataset, we evaluated ICS addition in the dual bronchodilator group compared with the triple therapy group.

Study Outcome

The study outcome was the time to the first composite events including moderate-to-severe exacerbation, all-cause mortality, and any pneumonia event. Moderate exacerbations were defined as any exacerbation events requiring treatment with systemic glucocorticoids or antibiotics. Severe exacerbations were defined as exacerbation events associated with hospitalization. Pneumonia events were diagnosed by new infiltrations on chest imaging, respiratory symptoms and signs on physical examination, or laboratory findings.

Candidate Prediction Factors for the Use of ICSs in the Prediction Scoring Model

Based on prior knowledge of associations with the composite event, the following demographic and laboratory variables were examined as candidate prediction factors for the prediction scoring model: age, sex, race, body mass index, smoking status, exacerbation history of COPD in the previous year (including moderate exacerbation, severe exacerbation, and steroid-requiring exacerbation), pulmonary function testing, reversibility (defined as an increase in FEV_1 of ≥12% and ≥200 mL after the use of albuterol), CAT score, and blood eosinophil count.[11–14]

Statistical Analysis: Development of the Prediction Scoring Model

To develop the prediction scoring model, we used the dataset of the IMPACT study, which is one of the important, large randomized controlled studies that compared the efficacy between triple therapy and dual bronchodilator therapy in patients with COPD.[6] The ultimate goal of the prediction scoring model was to provide personalized information about 1) whether withdrawing ICSs from triple therapy would increase the risk of developing the composite events and 2) whether adding ICSs to the currently used dual bronchodilators would decrease this risk. The development of the prediction model consisted of three steps. In step 1, as an initial screening process, each candidate prediction factor was examined for its association with the composite events using Cox proportional hazards regression models, and the predictors with a *P*-value <0.05 in any model were selected for further consideration. In step 2, using interaction analyses, we focused on identifying subgroups where an effect by ICS use would differ. Including an interaction effect with treatment also allowed the predicted survival risk to vary by treatment regimen. Interaction effects between the treatment and each prediction factor were assessed one at a time, while adjusting for the other factors. Predictors with *P*-value <0.2 for interaction (sex, race, previous exacerbation, and blood eosinophil count) were included in the final model. In step 3, we added marginal effects (ie, a prediction factor was added to the model without a treatment interaction term) to improve the risk prediction accuracy. In step 3, the prediction scoring model further included the marginal effects with *P*-value <0.05 (COPD duration, exacerbation history requiring treatment with systemic steroids, FEV_1). The weights of the prediction score were derived from regression coefficients of the coefficient-based score. For easier interpretation and implementation, we simplified the weights as 'points', where the weights were divided by the lowest regression coefficients of all prediction factors chosen and rounded to the nearest integer. A brief algorithm for the development of the prediction scoring model is presented in Supplemental Figure 1.

The predictive performance of the developed prediction scoring model, which consisted of COPD duration, history of Acute exacerbation, Sex, Pulmonary function tests, blood Eosinophil count, and Race (CASPER model), was evaluated through both ICS withdrawal and ICS addition datasets. The discrimination capability of the CASPER model was assessed using Harrell's C-index and area under the time-dependent receiver operating characteristic curve (time-dependent AUC) every 60 days after the randomization date.[15,16] Model calibration was evaluated using plots comparing the predicted risks with the observed counterparts. A coefficient-based score was compared with the CASPER model as proof of no loss of information due to the simplified points. We also compared Harrell's C-index of the CASPER model with that of the combined criteria of both blood eosinophil count and history of moderate-to-severe exacerbation in the past year, which were regarded as the effective criteria that guide clinicians to prescribe ICSs or not. In addition, the prediction was compared with the following models: 1) blood eosinophil count + history of moderate-to-severe exacerbation in the past year + CAT score, 2) simplified model 1: FEV_1 + number of moderate-to-severe exacerbations in the past year + sex + blood eosinophil count and interaction effects, and 3) simplified model 2: FEV_1 + number of moderate-to-severe exacerbations in the past year + sex + blood eosinophil count without interaction effects. Optimism for the internal validation was corrected using the bootstrapping approach. To assess the calibration capability of the CASPER model, patients were divided into six risk groups based on the total points (ie, 15th, 30th, 50th, 70th, and 85th percentiles of the total points). Then, the model calibration was assessed using calibration plots comparing the predicted and observed survival risk at 180 and 360 days, where the predicted survival risk was calculated from the scores derived from the CASPER model, and the observed survival risk was calculated using the Kaplan–Meier estimation method. All analyses were performed using R statistical software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Subjects

The patient selection flow is shown in Figure 1. In the IMPACT study, we analyzed 2389 subjects who were previously using triple therapy before enrollment in the ICS withdrawal dataset and 540 subjects who were previously using dual bronchodilator before enrollment in the ICS addition dataset. In the ICS withdrawal dataset, 1566 subjects were treated with triple therapy, and 823 subjects were with dual bronchodilators during the study period. In the ICS addition dataset, 357 subjects and 183 subjects were treated with triple therapy and dual bronchodilators, respectively.

The baseline characteristic of the ICS withdrawal and ICS addition datasets are described in Table 1 and Supplemental Table 1, respectively. There was no significant difference in the baseline characteristics between the triple therapy and dual bronchodilator therapy groups in the ICS withdrawal dataset. However, we found an imbalance in baseline characteristics between the two groups in the ICS addition dataset. There were more subjects with a history of three or more moderate-to-severe exacerbations in the past year in the dual bronchodilator therapy group than in the triple therapy group in the ICS addition dataset. Subjects in the ICS withdrawal dataset had a longer COPD duration, more frequent history of exacerbation, worse FEV_1, and higher blood eosinophil count than those in the ICS addition dataset (Table 2).

Study Outcomes

Regarding the study outcomes, the composite events occurred in 60.1% of subjects in the ICS withdrawal dataset (59.3% in the triple therapy group vs 61.5% in the dual bronchodilator therapy group) and in 52.4% of subjects in the ICS addition dataset (52.9% vs 51.4%) within 12 months (Table 3). Six-month composite events occurred in 46.0% of the subjects in the withdrawal dataset (43.8% vs 50.2%) and 37.2% in the ICS addition dataset (35.6% vs 40.4%).

Development of the Prediction Scoring Model

The results of the marginal and interaction analyses for the composite events within 12 months are presented in Table 4. Multivariable Cox proportional hazards regression analysis with the final set of prediction factors showed that the estimated hazard ratios (HRs) of the risk of the composite events were the same for COPD duration, number of exacerbations requiring treatment with systemic steroids in the previous year, and FEV_1 in either treatment regimen. However, the estimated HRs were different between the two treatment regimens in terms of sex, race, number of

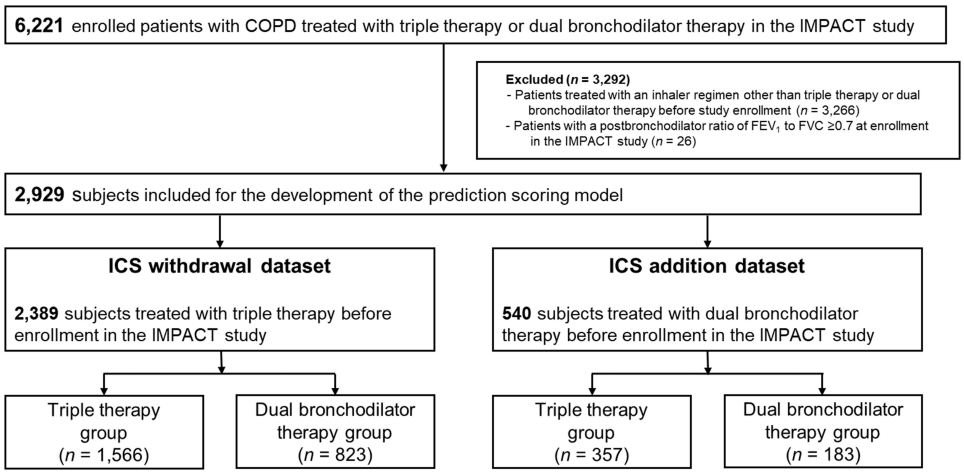

Figure 1 Subject selection flowchart. Researchers selected 4151 patients from the triple therapy group (combination of fluticasone furoate, umeclidinium, and vilanterol) and 2070 patients from the dual bronchodilator therapy group (umeclidinium and vilanterol) of the IMPACT study. The study subjects were further restricted to those who were using triple therapy or dual bronchodilator therapy before study enrollment. A total of 2929 subjects were assigned to the ICS withdrawal and ICS addition datasets according to the inhaler regimen before study enrollment.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2-agonist.

Table 1 Baseline Characteristics of the Study Subjects in the ICS Withdrawal Dataset

Variables	Overall (*n* = 2389)	Triple Therapy (*n* = 1566)	Dual Bronchodilator Therapy (*n* = 823)	*P*-value
Age, years	65.7 (8.0)	65.6 (8.0)	65.9 (8.0)	0.410
Sex				0.839
Male	1574 (65.9%)	1034 (66.0%)	540 (65.6%)	
Female	815 (34.1%)	532 (34.0%)	283 (34.4%)	
Race				0.847
White	1921 (80.4%)	1261 (80.5%)	660 (80.2%)	
Other	468 (19.6%)	305 (19.5%)	163 (19.8%)	
Body mass index (kg/m^2)	26.6 (6.2)	26.8 (6.3)	26.3 (5.9)	0.059
Smoking history				0.078
Current smoker	729 (30.5%)	459 (29.3%)	270 (32.8%)	
Former smoker	1660 (69.5%)	1107 (70.7%)	553 (67.2%)	
Time since first COPD diagnosis				0.238
<1 year	92 (3.9%)	57 (3.6%)	35 (4.3%)	
≥1 year to <5 years	686 (28.7%)	431 (27.5%)	255 (31.0%)	
≥5 years to <10 years	821 (34.4%)	546 (34.9%)	275 (33.4%)	
≥10 years	790 (33.1%)	532 (34.0%)	258 (31.3%)	
COPD exacerbation in the previous year				0.464
0–1	1130 (47.3%)	741 (47.3%)	389 (47.3%)	
2	926 (38.8%)	616 (39.3%)	310 (37.7%)	
3 or more	333 (13.9%)	209 (13.3%)	124 (15.1%)	
≥2 moderate or ≥1 severe exacerbation in the previous year				0.703
Yes	1666 (69.7%)	1088 (69.5%)	578 (70.2%)	
No	723 (30.3%)	478 (30.5%)	245 (29.8%)	
COPD exacerbation requiring systemic steroid in the previous year				0.798
0	344 (14.4%)	230 (14.7%)	114 (13.9%)	
1	1194 (50.0%)	776 (49.6%)	418 (50.8%)	
2 or more	851 (35.6%)	560 (35.8%)	291 (35.4%)	
Pulmonary function test				
FEV_1, L	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	0.696
FEV_1% predicted	42.6 (13.9)	42.5 (13.9)	42.7 (13.9)	0.715
FVC, L	2.7 (0.8)	2.7 (0.8)	2.7 (0.8)	0.590
FEV_1/FVC	0.45 (0.11)	0.45 (0.11)	0.44 (0.11)	0.876
Reversibility	395 (16.5%)	255 (16.3%)	140 (17.0%)	0.808
CAT score	20.3 (6.2)	20.2 (6.2)	20.4 (6.2)	0.599
Blood eosinophil count (10^9 cells per L)				0.735
<0.1	604 (25.3%)	397 (25.4%)	207 (25.2%)	
≥0.1 to <0.3	1274 (53.3%)	838 (53.5%)	436 (53.0%)	
≥0.3	509 (21.3%)	329 (21.0%)	180 (21.9%)	

Notes: Categorical variables are presented as number with percentages of the subjects, and continuous variables are presented as the mean with standard deviation. *P*-values were calculated by chi-square tests or Student's *t*-tests for the comparison between the two groups of triple therapy and dual bronchodilator therapy. Reversibility was defined as an increase in FEV_1 of ≥12% and ≥200 mL after use of albuterol.

Abbreviations: CAT, chronic obstructive pulmonary disease assessment test; COPD, Chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Table 2 Baseline Characteristics of the Study Subjects in the ICS Withdrawal and ICS Addition Datasets

Variables	ICS Withdrawal Dataset (n = 2389)	ICS Addition Dataset (n = 540)	*P*-value
Age, years	65.7 (8.0)	65.7 (8.4)	0.974
Sex			0.182
Male	1574 (65.9%)	372 (68.9%)	
Female	815 (34.1%)	168 (31.1%)	
Race			0.785
White	1921 (80.4%)	437 (80.9%)	
Other	468 (19.6%)	103 (19.1%)	
Time since first COPD diagnosis			0.004
<1 year	92 (3.9%)	36 (6.7%)	
≥1 year	2297 (96.1%)	504 (93.3%)	
COPD exacerbation in the previous year			0.020
0–2	2056 (86.1%)	485 (89.8%)	
3 or more	333 (13.9%)	55 (10.2%)	
COPD exacerbation requiring systemic steroid in the previous year			<0.001
0	344 (14.4%)	120 (22.2%)	
1	1194 (50.0%)	260 (48.1%)	
2 or more	851 (35.6%)	160 (29.6%)	
FEV_1% predicted			<0.001
<30	472 (19.8%)	73 (13.5%)	
≥30 to <50	1246 (52.2%)	281 (52.0%)	
≥50	671 (28.1%)	186 (34.4%)	
Blood eosinophil count (10^9 cells per L)			0.006
<0.1	604 (25.3%)	105 (19.4%)	
≥0.1 to <0.3	1276 (53.4%)	325 (60.2%)	
≥0.3	509 (21.3%)	110 (20.4%)	

Notes: Categorical variables are presented as number with percentages of the subjects, and continuous variables are presented as the mean with standard deviation. *P*-values were calculated by chi-square tests or Student's *t*-tests. Composite events included moderate-to-severe exacerbation, all-cause mortality, and pneumonia.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 sec.

Table 3 Frequency of Composite Events at 6 and 12 Months

	ICS Withdrawal Dataset			ICS Addition Dataset		
	Overall (n = 2389)	Triple Therapy (n = 1566)	Dual Bronchodilator Therapy (n = 823)	Overall (n = 540)	Triple Therapy (n = 357)	Dual Bronchodilator Therapy (n = 183)
Composite events						
6 months	1099 (46.0%)	686 (43.8%)	413 (50.2%)	201 (37.2%)	127 (35.6%)	74 (40.4%)
12 months	1435 (60.1%)	929 (59.3%)	506 (61.5%)	283 (52.4%)	189 (52.9%)	94 (51.4%)

Notes: The frequency of composite events at 6 and 12 months is presented as a number with a percentage of the subjects. Composite events included moderate-to-severe exacerbation, all-cause mortality, and pneumonia.

moderate-to-severe exacerbation episodes in the previous year, and blood eosinophil count. Based on this result, we developed a coefficient-based score shown in Supplemental Table 2, and its mathematical formula in the final Cox model that estimated relative risk of the composite event is presented in Supplemental Material 1.

Table 4 Marginal and Interaction Analyses of the Composite Events in the ICS Withdrawal Dataset

Variables	Marginal Analysis		Interaction Analysis		
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P*-value for Interaction
COPD treatment					
Triple therapy	Reference				
Dual bronchodilators	1.23 (1.11–1.38)	<0.001			
Age					0.265
<65 years	Reference		1.153 (0.979–1.356)	0.088	
≥65 years	0.99 (0.89–1.11)	0.886	1.305 (1.128–1.510)	<0.001	
Sex					0.111
Female	Reference		1.385 (1.160–1.653)	<0.001	
Male	0.74 (0.66–0.83)	<0.001	1.154 (1.007–1.324)	0.040	
Race					0.014
Other	Reference		0.922 (0.712–1.195)	0.541	
White	1.16 (1.01–1.34)	0.037	1.318 (1.170–1.485)	<0.001	
Smoking history					0.903
Current smoker	Reference		1.222 (1.007–1.483)	0.043	
Former smoker	1.07 (0.95–1.20)	0.270	1.240 (1.088–1.413)	0.001	
COPD duration					0.251
<1 year	Reference		0.850 (0.446–1.623)	0.623	
≥1 year	1.49 (1.09–2.04)	0.013	1.248 (1.118–1.394)	<0.001	
Exacerbation in the previous year					0.147
<3	Reference		1.190 (1.056–1.341)	0.004	
≥3	1.47 (1.27–1.71)	<0.001	1.469 (1.135–1.901)	0.003	
Exacerbation requiring systemic steroid in the previous year					0.371
0	Reference		1.192 (0.866–1.640)	0.281	
1	1.22 (1.03–1.45)	0.021	1.153 (0.988–1.347)	0.071	
2 or more	1.40 (1.17–1.67)	<0.001	1.360 (1.144–1.616)	<0.001	
FEV_1 (%) predicted					0.835
<30	Reference		1.226 (0.972–1.548)	0.086	
≥30 to <50	0.75 (0.66–0.85)	<0.001	1.269 (1.093–1.474)	0.002	
≥50	0.58 (0.50–0.68)	<0.001	1.172 (0.945–1.453)	0.148	
CAT score					0.969
<20	Reference		1.237 (1.056–1.449)	0.008	
≥20	1.02 (0.92–1.14)	0.716	1.232 (1.061–1.430)	0.006	
Blood eosinophil count (10^9 cells per L)					0.017
<0.1	Reference		1.009 (0.806–1.262)	0.940	
≥0.1 to <0.3	1.04 (0.91–1.18)	0.585	1.211 (1.041–1.408)	0.013	
≥0.3	1.42 (1.22–1.65)	<0.001	1.586 (1.274–1.975)	<0.001	

Notes: Marginal and interaction analyses were performed using Cox proportional hazards regression models to investigate clinical factors that would modify the effect of inhaled corticosteroid use on the composite events. For simplicity, predictive factors with *P*-value >0.2 (age, smoking, and COPD assessment test score) in the multivariable marginal analysis were further excluded from the final model.

Abbreviations: CAT, chronic obstructive pulmonary disease assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 sec; HR, hazard ratio.

Table 5 The CASPER Model of the Composite Events

Variables	Triple Therapy	Dual Bronchodilator Therapy
Baseline score due to treatment regimen	0	−2
Sex		
Male	0	0
Female	1.5	2
Race		
Other	0	0
White	0	2
COPD duration		
<1 year	0	0
≥1 year	2	2
Number of moderate-to-severe exacerbations in the previous year		
<3	0	0
≥3	2	3
Number of exacerbations requiring systemic steroids in the previous year		
0	0	0
1	1	1
≥2	2	2
FEV_1% predicted		
≥50	0	0
≥30 and <50	1.5	1.5
<30	3	3
Blood eosinophil count (10^9 cells/L)		
<0.1	0	0
≥0.1 to <0.3	0	1
≥0.3	1	3.5

Notes: The weights were divided by the lowest regression coefficients of all predictors chosen and rounded to the nearest integer. In the CASPER Model, the score ranges from 0 to 11.5 with triple therapy and from −2 to 15.5 with the dual bronchodilator therapy.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 sec.

In the simplified prediction scoring model (CASPER model, shown in Table 5), the score ranges from 0 to 11.5 with triple therapy and from −2 to 15.5 with dual bronchodilator therapy. The correlation between the coefficient-based score and the CASPER model was 0.99 in both the ICS withdrawal and ICS addition datasets. Sample calculations for the CASPER model are provided in the Discussion section.

Predictive Performance of the Prediction Scoring Model

Harrell's C-indexes of the coefficient-based score in the ICS withdrawal and ICS addition datasets were 0.600 (95% confidence interval (CI)=0.584–0.615, *P*-value <0.001) and 0.589 (95% CI = 0.555–0.622, *P*-value <0.001), respectively, indicating good performance in both datasets. Harrell's C-index of the CASPER model was in line with that of the coefficient-based score (Table 6). The CASPER model (0.599, 95% CI = 0.584–0.614, *P*-value <0.001 in the ICS withdrawal dataset and 0.592, 95% CI = 0.558–0.625, *P*-value <0.001 in the ICS addition dataset) presented better discrimination capability than the model including the blood eosinophil count and history of moderate-to-severe exacerbation in the previous year (0.524, 95% CI: 0.512-0.534, *P*-value <0.001, *P*-value compared with the CASPER model <0.001 in the ICS withdrawal dataset and 0.533, 95% CI = 0.511–0.555, *P*-value = 0.003, *P*-value compared with

Table 6 Model Discrimination Evaluation with Harrell's C-Index

	Overall Population			Triple Therapy Group			Dual Bronchodilator Therapy Group		
	Harrell's C-Index (95% CI)	***P*-value**	***P*-value for Comparison With the CASPER Model**	**Harrell's C-Index (95% CI)**	***P*-value**	***P*-value for Comparison With the CASPER Model**	**Harrell's C-Index b (95% CI)**	***P*-value**	***P*-value for Comparison With the CASPER Model**
ICS withdrawal dataset									
CASPER Model	0.599 (0.584, 0.614)	<0.001		0.579 (0.560, 0.598)	<0.001		0.621 (0.596, 0.647)	<0.001	
Exacerbation history + BEC	0.524 (0.513, 0.534)	<0.001	<0.001	0.512 (0.499, 0.524)	0.077	<0.001	0.545 (0.527, 0.564)	<0.001	<0.001
Exacerbation history + BEC + CAT score	0.516 (0.507, 0.524)	<0.001	<0.001	0.512 (502, 0.522)	0.021	<0.001	0.522 (0.508, 0.536)	0.002	<0.001
Simplified Model 1	0.592 (0.577, 0.608)	<0.001	0.102	0.578 (0.559, 0.597)	<0.001	0.837	0.607 (0.581, 0.633)	<0.001	0.025
Simplified Model 2	0.590 (0.575, 0.606)	<0.001	0.046	0.577 (0.588, 0.596)	<0.001	0.771	0.602 (0.577, 0.628)	<0.001	0.007
ICS addition dataset									
CASPER Model	0.592 (0.558, 0.625)	<0.001		0.582 (0.541, 0.623)	<0.001		0.602 (0.547, 0.657)	<0.001	
Exacerbation history + BEC	0.533 (0.511, 0.555)	0.003	<0.001	0.529 (0.503, 0.555)	0.028	0.021	0.541 (0.500, 0.581)	0.049	0.043
Exacerbation history + BEC + CAT score	0.524 (0.509, 0.539)	0.002	<0.001	0.527 (0.509, 0.546)	0.003	0.015	0.517 (0.490, 0.543)	0.221	0.004
Simplified Model 1	0.584 (0.550, 0.618)	<0.001	0.439	0.565 (0.524, 0.607)	0.002	0.187	0.606 (0.551, 0.662)	<0.001	0.804
Simplified Model 2	0.574 (0.541, 0.608)	<0.001	0.076	0.561 (0.520, 0.602)	0.003	0.085	0.590 (0.535, 0.646)	0.001	0.492

Notes: Harrell's C-index was used to assess the discrimination capability of the CASPER model. Both developed models presented higher discrimination capability than the history of acute exacerbation in the previous year and blood eosinophil count. We defined exacerbation history when patients had more than two moderate exacerbation events or one severe exacerbation event in the previous year. We structured two simplified models to compare the C-index. In simplified model 1, the FEV_1, number of the moderate-to-severe exacerbations in the past year, sex, and blood eosinophil count were included as prediction factors and considered interaction effects with therapy. Simplified model 2 included same prediction factors but not considered the interaction effects with therapy.

Abbreviations: BEC, blood eosinophil count; CAT, chronic obstructive pulmonary disease assessment test; FEV_1, forced expiratory volume in 1 sec; ICS, inhaled corticosteroid.

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the CASPER model <0.001 in the ICS addition dataset). It also showed better discrimination capability than the model including the blood eosinophil count, history of moderate-to-severe exacerbation in the previous year, and CAT score (0.516, 95% CI = 0.507–0.524, *P*-value <0.001, *P*-value compared with the CASPER model <0.001 in the ICS withdrawal dataset and 0.524, 95% CI = 0.509–0.539, *P*-value = 0.002, *P*-value compared with the CASPER model <0.001 in the ICS addition dataset). Harrell's C-index of the CASPER model was significantly higher than those of the aforementioned models regardless of the treatment regimen (triple therapy group or dual bronchodilator therapy group). When we compared the C-index between developed CASPER model and the simplified model, there was a significant difference in the ICS withdrawal effect from triple therapy. Time-dependent receiver operating characteristic curves of the coefficient-based score and CASPER model are presented in Figure 2.

Calibration Performance of the Prediction Scoring Model

The calibration performance of the coefficient-based score and CASPER model in Supplemental Tables 3 and Table 7. The time-dependent AUC at 180 and 360 days of the coefficient-based score and CASPER model are also presented in Figure 2. The results for the CASPER model were 0.608 to 0.624 and 0.586 to 0.617 in the ICS withdrawal and ICS addition datasets, respectively. The calibration plots in Figure 3 show a good correlation between the predicted and observed risks with the CASPER model in both the ICS withdrawal and ICS addition datasets. The predicted and observed survival risk of the coefficient-based score and simplified models 1 and 2 are shown in Supplemental Tables 4, and 5.

Discussion

In this study, we developed the prediction scoring model, the CASPER model, to estimate the risk of composite events when patients with COPD were managed with triple therapy or dual bronchodilator therapy. Although the prediction performance was not fully satisfied, the CASPER model showed a statistically significant and higher Harrell's C-index than the combined criteria of both the blood eosinophil count and history of moderate-to-severe exacerbation in the past year, which are regarded as important indicators for the use of ICSs.[2] We constructed the composite events as the

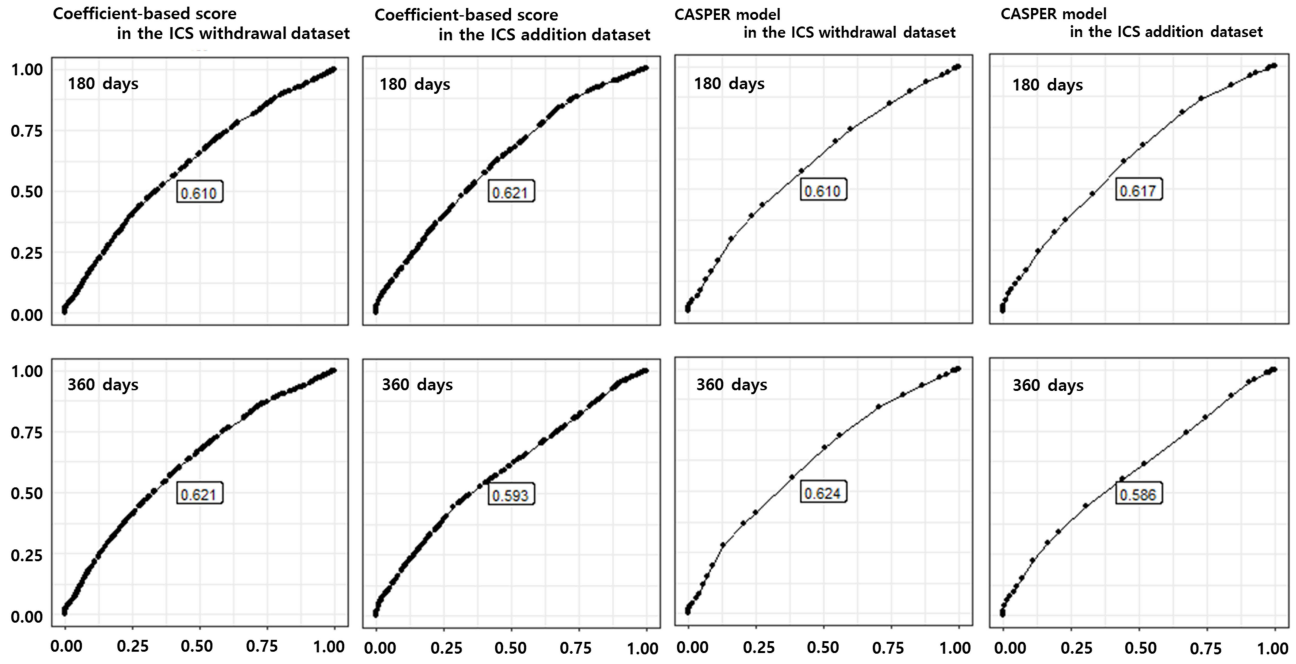

Figure 2 Time-dependent receiver operating characteristic curves of the coefficient-based score and CASPER model. We investigated the discrimination capability of the coefficient-based score and CASPER model for composite events using the area under the time-dependent receiver operating characteristic curves at 180 and 360 days after the randomization date. Composite events included moderate-to-severe exacerbation, all-cause mortality, and pneumonia. Both models presented a similar discrimination capability, regardless of the study population analyzed.
Abbreviation: ICS, inhaled corticosteroid.

Table 7 Calibration Performance of the CASPER Model

Score	Overall Population		Triple Therapy Group		Dual Bronchodilator Therapy Group	
	Predicted Survival	Observed Survival	Predicted Survival	Observed Survival	Predicted Survival	Observed Survival
Inhaled corticosteroid withdrawal dataset						
180 days						
<4	0.686	0.684 (0.635–0.736)	0.679	0.692 (0.632–0.757)	0.692	0.669 (0.587–0.763)
≥4 and <5	0.612	0.608 (0.563–0.655)	0.613	0.617 (0.569–0.670)	0.609	0.563 (0.462–0.686)
≥5 and <6	0.555	0.534 (0.487–0.585)	0.561	0.527 (0.470–0.590)	0.546	0.549 (0.469–0.642)
≥6 and <7	0.509	0.531 (0.485–0.581)	0.520	0.555 (0.502–0.614)	0.491	0.463 (0.378–0.567)
≥7 and <8	0.439	0.427 (0.376–0.483)	0.452	0.423 (0.362–0.494)	0.427	0.434 (0.353–0.535)
≥8	0.302	0.329 (0.283–0.382)	0.345	0.353 (0.278–0.447)	0.277	0.314 (0.259–0.382)
360 days						
<4	0.550	0.548 (0.496–0.606)	0.527	0.533 (0.469–0.605)	0.583	0.576 (0.490–0.676)
≥4 and <5	0.459	0.448 (0.403–0.498)	0.445	0.448 (0.399–0.504)	0.484	0.448 (0.347–0.577)
≥5 and <6	0.393	0.373 (0.328–0.424)	0.384	0.356 (0.303–0.419)	0.412	0.409 (0.331–0.505)
≥6 and <7	0.342	0.353 (0.309–0.403)	0.339	0.353 (0.303–0.413)	0.353	0.353 (0.272–0.457)
≥7 and <8	0.271	0.273 (0.229–0.327)	0.269	0.253 (0.201–0.320)	0.288	0.312 (0.237–0.411)
≥8	0.154	0.177 (0.141–0.224)	0.173	0.205 (0.144–0.292)	0.159	0.162 (0.119–0.219)
Inhaled corticosteroid addition dataset						
180 days						
<4	0.754	0.793 (0.722–0.870)	0.769	0.816 (0.740–0.899)	0.761	0.708 (0.548–0.916)
≥4 and <5	0.698	0.682 (0.600–0.777)	0.704	0.658 (0.564–0.767)	0.702	0.773 (0.616–0.969)
≥5 and <6	0.656	0.637 (0.547–0.741)	0.655	0.591 (0.483–0.722)	0.659	0.744 (0.605–0.916)
≥6 and <7	0.618	0.643 (0.544–0.761)	0.608	0.686 (0.572–0.821)	0.619	0.544 (0.370–0.800)
≥7 and <8	0.563	0.575 (0.466–0.711)	0.537	0.519 (0.373–0.720)	0.569	0.638 (0.487–0.835)
≥8	0.442	0.390 (0.281–0.541)	0.420	0.440 (0.244–0.795)	0.447	0.376 (0.255–0.554)
360 days						
<4	0.591	0.546 (0.462–0.645)	0.588	0.558 (0.465–0.671)	0.647	0.500 (0.335–0.746)
≥4 and <5	0.511	0.505 (0.418–0.611)	0.490	0.496 (0.398–0.617)	0.568	0.545 (0.372–0.799)
≥5 and <6	0.456	0.517 (0.425–0.629)	0.423	0.435 (0.330–0.574)	0.513	0.709 (0.564–0.891)
≥6 and <7	0.407	0.432 (0.332–0.563)	0.363	0.432 (0.316–0.590)	0.464	0.440 (0.270–0.715)
≥7 and <8	0.342	0.367 (0.265–0.508)	0.282	0.275 (0.158–0.479)	0.406	0.470 (0.321–0.687)
≥8	0.223	0.176 (0.097–0.318)	0.174	0.073 (0.011–0.483)	0.280	0.214 (0.117–0.393)

Notes: The predicted versus observed survival risk of the CASPER model at 180 and 360 days are presented. The predicted survival risk were calculated from the score derived from the CASPER model, and the observed survival risk were calculated using Kaplan–Meier estimation.

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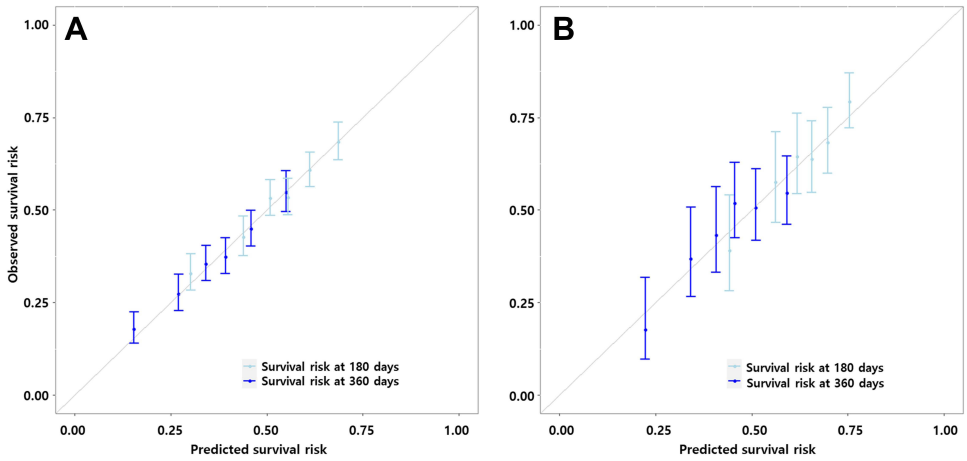

Figure 3 Calibration plots of the CASPER model. Calibration plots comparing the predicted and observed probability of composite events in (**A**) for the ICS withdrawal dataset and (**B**) for the ICS addition dataset at 180 (sky-blue line) and 360 (blue line) days. We presented observed survival risk and confidence interval (y-axis) at each predicted risk (x-axis) of six groups according to the scores. The calibration curves showed a good correlation between the predicted and observed survival risk of composite events in both datasets.
Abbreviations: ICS, inhaled corticosteroid.

study outcome to assess the integrated beneficial effect (ie, efficacy and adverse effects together) of ICSs use. To the best of our knowledge, no study has comprehensively predicted the beneficial effect of withdrawing ICSs from triple therapy and adding ICSs to treatment with dual bronchodilators. Although a previous study has developed a prediction scoring model, the model compared the clinical exacerbation risk between ICS-LABA and LABA only regimens.[17] However, there were limitations in the results for clinicians because the LAMA only regimen is more commonly recommended and prescribed than the LABA only regimen due to its favorable treatment efficacy and safety profiles.[18–20] Other studies have only investigated the association between ICS response and each predictor, including blood eosinophil count, age, and history of exacerbation in the past year.[2,13,21] Compared with previous studies, our developed CASPER model could help clinicians predict the beneficial effects of ICS by comprehensively considering various characteristics of patients with COPD that can be easily measured during routine clinic visits.

We developed the CASPER model using data from patients who had used triple therapy before enrollment in the IMPACT study. Therefore, this model might be suitable for predicting the risk of composite events in patients considering withdrawal of ICSs from triple therapy. We additionally tried to investigate the effectiveness of this model for patients considering the addition of ICSs to dual bronchodilator therapy. For this purpose, this model was applied to subjects who had used dual bronchodilator therapy before enrollment. The Harrell's C-index of the developed CASPER model within the ICS addition dataset was in line with that in the ICS withdrawal dataset. These results indicated that the developed CASPER model might be applied to both dual bronchodilator and triple therapy groups to guide the addition or withdrawal of ICSs.

In the developed CASPER model, four prediction factors, including sex, race, number of moderate-to-severe exacerbations in the previous year, and blood eosinophil count affected the risk of composite events. This implies that, for the two patients with different characteristics for of these four prediction factors, the predicted risk caused by the additional ICS use will not be the same. Among these four prediction factors, the blood eosinophil count most highly affected the risk of composite events. In patients with blood eosinophil count of $\geq 0.3 \times 10^9$ cells/L, triple therapy was associated with a lower incidence of composite events than dual bronchodilator therapy, regardless of other prediction factors. For example, White female patients with ≥3 exacerbation episodes in the previous year and blood eosinophil count $\geq 0.3 \times 10^9$ cells/L could have the highest risk if ICSs were withdrawn from treatment. This is in accordance with the recommendation of the GOLD guidelines and the results of previous studies showing favorable outcomes of triple therapy in patients with a higher blood eosinophil count.[2,6–8,22]

Among the four aforementioned prediction factors, there was no clear evidence showing that the response to triple therapy and dual bronchodilator therapy differed depending on sex and race. Schermer et al reported that female ICS

users presented a higher risk of COPD exacerbation than male ICS users in case of ICS withdrawal.[8] Conversely, in a Taiwanese nationwide cohort study, the pneumonia risk was less in female patients using ICSs for COPD than in their male counterparts.[23] These findings might favor triple therapy over dual bronchodilator therapy for female patients. Cole et al reported that ICS cessation was more successful in patients of South Asian origin than White patients.[24] To clarify the association of sex and race with the beneficial effects of ICSs in patients with COPD, further studies would be needed.

Although the score for COPD duration, number of exacerbations requiring treatment with systemic steroids in the previous year, and FEV_1% predicted were similar between the triple therapy and dual bronchodilator therapy groups, an interaction was observed between each prediction factor and inhaler regimen. To reflect these interactions, we assigned −2 points for dual bronchodilator therapy. For example, assuming a White woman presented with a history of ≥3 episodes of moderate-to-severe exacerbations not requiring treatment with systemic steroids in the previous year and a blood eosinophil count of 0.25×10^9 cells/L, if she presented with a FEV_1 of 60% predicted and a COPD duration <1 year, she would have 4.5 points for triple therapy and 8.5 points for dual bronchodilator therapy. If clinicians consider withdrawing ICS from the triple therapy regimen, the predicted probability without composite events at 360 days would be 0.459 with triple therapy and 0.154 with dual bronchodilator therapy. If the same woman required systemic steroids for exacerbations in the previous year, had COPD for >20 years, and presented with a FEV_1 25% of predicted, she would have 11.5 points for triple therapy and 15.5 points for dual bronchodilator therapy. In this case, there would be no difference between triple therapy and dual bronchodilator therapy because both scores are included in the highest risk group.

In this study, the CASPER model presented good but insufficient Harrell's C-indexes. In our opinion, two crucial points had an effect on the relatively low C-index. At first, the study population for development was included in a large randomized controlled study and had relatively similar characteristics compared with the real-world population. This similarity might have made the difference smaller than the real effect. In addition, because composite events included both exacerbation events, which were expected to be reduced by ICS use, and pneumonia, which was expected to be increased by ICS use, the C-index of the developed model might have been reduced. However, this model presented higher C-index than the combined criteria of both history of exacerbation in the previous year and blood eosinophil count. In the GOLD guidelines, patients with a history of ≥1 episode of severe exacerbation or ≥2 moderate exacerbations in the previous year or a high blood eosinophil count were recommended to use ICSs.[2] However, when we applied these criteria to the study subjects, Harrell's C-index was only approximately 0.5 in each prediction factor. These results indicated that the use of ICSs might be determined by considering various prediction factors rather than only one. In addition, other models including important prediction factors for ICS use in patients with COPD also presented a lower C-index than those in the developed CASPER model. Furthermore, a C-index of approximately 0.6 does not necessarily imply poor predictive performance since the magnitude of the C-index is determined by other aspects with respect to survival outcomes. Therefore, the C-index may not be optimal in assessing prediction models, and calibration is as important for accurately predicting the risk.[25] The calibration results shown in Table 7 demonstrate that the predicted risks were close to the observed risks, suggesting that the prediction errors were acceptable.

There were several limitations to this study. First, the developed CASPER model did not present a sufficient C-index. As previously mentioned, this model presented a higher C-index than the history of moderate-to-severe exacerbation in the previous year and blood eosinophil count. A history of moderate-to-severe exacerbation in the previous year and blood eosinophil count are regarded as important prediction factors for ICS use in patients with COPD; therefore, this model could help clinicians to determine whether patients with COPD require ICS prescription or not. Second, the model did not directly guide the need for triple therapy or dual bronchodilator therapy. This model could only predict the probability of composite events depending on whether the subjects use triple therapy or dual bronchodilator therapy. Third, we developed the prediction scoring model using only subjects enrolled in the IMPACT study. We used a dataset from a previously performed study and did not perform prospective validation; therefore, this study had the nature of a retrospective study. Patients enrolled in the IMPACT study had a history of moderate-to-severe exacerbation and higher CAT score. Therefore, the CASPER model is more adequate for use among patients with severe COPD. To be applicable

to a wide range of patients and certified, the developed model should be applied to populations with varying characteristics in a large study with a prospective study design, and patients with mild COPD should be included.

Conclusions

In this study, the researchers developed a prediction scoring model, the CASPER model, to predict the effects of withdrawal or addition of ICSs among patients with COPD. Although the low C-index requires further validation in a large real-world population, clinicians might be able to calculate the probability of composite events when using triple therapy or dual bronchodilator therapy in patients with COPD by utilizing the CASPER model. Although not fully satisfactory, the CASPER model presented a favorable C-index compared with the blood eosinophil count and history of moderate-to-severe exacerbation in the previous year, which are regarded as important predictive factors for ICS use. The developed CASPER model might be applied for the prediction of the risk of composite events when considering the addition of ICSs to dual bronchodilator therapy or withdrawal of ICSs from triple therapy in patients with COPD.

Abbreviations

CAT, chronic obstructive pulmonary disease assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; time-dependent AUC, area under the time-dependent receiver operating characteristic curves.

Data Sharing Statement

The authors are not allowed to distribute the study data or are unable to deposit the data file used in this study in any openly accessible data repository.

Ethics Approval and Informed Consent

The study protocol was approved by the Institutional Review Board of the Asan Medical Centre (IRB no. 2021-0293) and complies with the Declaration of Helsinki. The board waived the requirement for obtaining patient informed consent because of the nature of the analysis. All provided data from the GlaxoSmithKline were anonymized and this study did not present any identifiable and private information.

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Disclosure

The authors report no conflicts of interest in this work.

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