CHEST Online Supplement

Association of Guideline-Recommended COPD Inhaler Regimens With Mortality, Respiratory Exacerbations, and Quality of Life

A Secondary Analysis of the Long-Term Oxygen Treatment Trial

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e-Appendix 1.

METHODS

Study Population

The Long-term Oxygen Treatment Trial (LOTT) was a randomized clinical trial that determined the efficacy of long-term supplemental oxygen among patients age 40 years or older with stable chronic obstructive pulmonary disease (COPD) and moderate resting or exercise induced hypoxemia.[1] The trial enrolled patients between January 2009 and August 2014 at 42 clinical sites across the United States. These sites included academic, community-affiliated, and Veteran Affairs medical centers. To be included in the trial, patients must have met all the following inclusion criteria:

- COPD predominant lung-disease
- ≥ 40 years of age
- ≥ 10 pack-year history of cigarette smoking
- mMRC score ≥ 1
- Post-bronchodilator FEV1/FVC ratio < 0.70
- Post-bronchodilator FEV1 ≤ 70% predicted or study physician determines presence of radiographic emphysema
- Resting SpO_2 89-93% **or** resting SpO_2 ≥ 94% with desaturation during exercise (SpO2 < 90% for at least 10 seconds during a six-minute walk test)
- Medicare Part A and B beneficiary or insurance willing to pay costs of study or patient willing to self-pay costs
- Approval by study physician for randomization to either group
- No exacerbation requiring new prescription of antibiotics or new/increased prescription of systemic corticosteroids in the 30 days prior to screening
- Willingness to discontinue pre-exist supplemental oxygen therapy if randomized to no long-term supplemental oxygen arm

In addition, patients who met any of the following criteria were excluded:

- COPD exacerbation between screening and randomization
- New prescription for supplemental oxygen between screening and randomization
- Thoracic surgery or other procedure likely to cause pulmonary instability within the prior 6 months
- Non-COPD lung disease that would affect survival or need for oxygen
- Epworth sleepiness scale score > 15
- Desaturation below 80% for at least 1 minute during a six-minute walk test (6MWT)
- Disease expected to cause death within 6 months of enrollment
- Participation in a different interventional study

LOTT followed patients until death or August 31st, 2015, whichever occurred first. Patients attended in-person visits at randomization and annually, during which study staff performed a detailed history, physical examination, and 6MWT. All patients completed spirometry at baseline. The trial conducted telephone interviews twice per year between in-person visits and mailed questionnaires to patients at 4 months and 16 months of follow-up. The trial determined vital status for all patients as of August 31st, 2015.

COPD Severity Assessment

We used the risk-stratification model proposed in the 2017 GOLD strategy to categorize patients into baseline disease severity groups **(e-Table 1)**.[2] Aiming to minimize recall bias, the LOTT trial did not collect historical, self-reported outpatient exacerbation data greater than 3 months prior to enrollment. We therefore considered patients to be high-risk for future respiratory exacerbations if they reported ≥ 1 outpatient exacerbation that required antibiotics or steroids in the 3 months prior to enrollment or had ≥ 1 exacerbation causing hospitalization in the preceding year.

Pneumonia

All exacerbation and serious adverse event data were reviewed by two authors (TLK and LJS) to discern possible cases of pneumonia. We defined pneumonia as any inpatient or outpatient encounter for which the primary/secondary diagnosis was "pneumonia" (including viral and aspiration pneumonia) and/or when specific treatment for pneumonia was administered. In the event of disagreement, a third author (LCF) reviewed cases to determine appropriateness for inclusion.

Statistical Analyses

We report baseline patient characteristics and inhaled medication use as frequencies for categorical variables and mean (standard deviation) for continuous variables.

We *a priori* hypothesized that future exacerbation risk, as measured by the disease severity assessment outlined above, would modify the association of patient-reported category of inhaled treatment (**e-Table 2**) with all time-to-event (primary composite, individual mortality and exacerbation) outcomes, follow-up 6MWT distance, and follow-up St. George Respiratory Questionnaire (SGRQ) score. We predicted that undertreatment would be more strongly associated with outcomes among high-risk (GOLD groups C/D) as compared to low-risk (GOLD groups A/B) patients. We therefore ran separate models across strata of future exacerbation risk (high vs. low) for all of analyses evaluating the primary exposure (category of inhaled treatment).

For our primary exposure, we generated separate multivariable Cox proportional-hazard models to estimate between-group hazard ratios for each time-to-event outcome. We censored for loss to follow-up and end of study. We *a priori* included covariates predicted to influence both the likelihood of receiving inhaled treatment and experiencing death or future exacerbations of COPD. After testing the proportional-hazards assumption using Schoenfeld residuals, we found that both GOLD stage severity of airflow obstruction and BODE Index violated this assumption. We therefore stratified all time-to-event models by these covariates.[3] Thus, for each time-to-event outcome, we ran separate models across strata of future exacerbation risk (high vs. low) and adjusted for baseline age, sex, Charlson score, smoking status, number of all-cause hospitalizations in the year prior to enrollment, and stratified by GOLD stage airflow obstruction and BODE Index. We additionally clustered all time-to-event models by clinical site to account for between-site variations in care quality.

We constructed generalized estimating equations using multivariable linear regression models to assess differences in mean follow-up 6MWT distance and SGRQ total score by category of inhaled treatment. We included patients with at least one follow-up measurement. We accounted for repeated measures using exchangeable correlation with robust variance estimators. To test for effect modification, we ran separate models across strata of future exacerbation risk (high vs low). We chose covariates *a priori*. In our final models, we adjusted for baseline outcome measure (6MWT or SGRQ score), age, sex, Charlson score, smoking status, GOLD stage airflow obstruction, BODE Index, and site. The β_1 coefficients reported from these models represent the mean difference in follow-up 6MWT distance (or SGRQ total score) among patients who reported inhaled regimens that undertreated or potentially overtreated when compared to those who reported regimens that aligned with recommendations in the 2017 GOLD strategy. We considered findings to have statistical significance at a p value of $\alpha < 0.05$.

Secondary Analyses

Propensity-Matched Analyses

We determined the association of patient-reported inhaled corticosteroid (ICS) use at baseline with the incidence of pneumonia among patients who were low-risk for future exacerbation (GOLD groups A/B). After restricting the cohort to patients in 2017 GOLD groups A/B, we propensity matched patients on the likelihood of receiving ICS at baseline with the goal of minimizing confounding by indication. We first developed a multivariable logistic regression model to assign propensity scores. We chose covariates *a priori* including age, sex, Charlson score, smoking status, BODE Index, GOLD stage airflow obstruction, and number of all-cause hospitalizations in the year prior to enrollment. We additionally clustered by site. We then matched patients 1:1 on the probability of ICS use via the nearest neighbor method (**e-Figure 2)**. We used a caliper size of 0.2*SE. Baseline characteristics of patients in the propensity matched cohort were similar between groups (**e-Table 3**).

We generated a negative binomial regression model with one binary covariate for ICS use to estimate the between-group incidence rate ratio for pneumonia. We prespecified a sensitivity analysis where, rather than propensity matching, we instead used a multivariable negative binomial regression model incorporating the above *a priori* chosen covariates to estimate the between-group incidence rate ratio for pneumonia.

GOLD 2011 Analyses

We reclassified patients' baseline disease severity according to recommendations in the 2011 GOLD strategy (**e-Table 4)**.[4] Compared with the 2017 GOLD disease severity assessment, the 2011 strategy incorporates GOLD stage severity of airflow obstruction into the determination of future exacerbation risk. In the 2011 classification, patients with an FEV_1 < 50% predicted are considered high-risk for future exacerbations irrespective of their history of prior exacerbations. For these analyses, we also classified inhaled regimens according to recommendations in the 2011 GOLD strategy (**e-Table 5)**. As with the 2017 strategy, most regimens that overtreated contained potentially unnecessary ICS. In contrast, the GOLD 2011 strategy was not prescriptive on the requirement for a long-acting bronchodilator across GOLD groups. Regimens aligned with recommendations in the 2011 strategy provided they contained a short-acting bronchodilator.

e-Table 1: COPD severity groups adapted from the 2017 GOLD strategy

Symptoms	Exacerbation Risk	
	Low-Risk[a] Prior Year: 0 COPD hospitalizations Past 3 months: 0 exacerbations	High-Risk[b] Prior Year: 1+ COPD hospitalizations Past 3 months: 1+ exacerbations
mMRC < 2	A	C
mMRC ≥ 2	B	D

[a] all criteria must be met
[b] the presence of any one of these criteria would categorize patients as high-risk
mMRC = Modified Medical Research Council dyspnea score

e-Table 2: Categorization of baseline inhaler regimen based on the 2017 GOLD strategy

2017 GOLD Group	Aligned	Not Aligned	
		Undertreated	Potentially Overtreated
A	SABD only or LABA only or LAMA only or LABA+LAMA	No inhaled therapy or ICS only	LABA+ICS or LAMA+ICS or LABA+LAMA+ICS
B	LABA only or LAMA only or LABA+LAMA	No inhaled therapy or SABD only or ICS only	LABA+ICS or LAMA+ICS or LAMA+LABA+ICS
C	LAMA only or LAMA+LABA or LABA+ICS LAMA+ICS	No inhaled therapy or SABD only or ICS only or LABA only	LABA+LAMA+ICS
D	LAMA only or LAMA+LABA or LABA+ICS or LAMA+ICS or LAMA+LABA+ICS	No inhaled therapy or SABD only or LABA only or ICS only	N/A

SABD = short-acting bronchodilator (includes short-acting beta agonist and short-acting muscarinic antagonists); LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid

e-Table 3: Baseline patient characteristics of the propensity matched cohort

Variable	Overall (n = 332)	ICS (n = 166)	No ICS (n = 166)
Demographics			
Age, mean [sd]	70.4 [7.4]	71.1 [7.2]	69.7 [7.5]
Male, n (%)	232 (69.9)	116 (69.9)	116 (69.9)
Current Smoker, n (%)	94 (28.3)	47 (28.3)	47 (28.3)
Comorbidities, n (%)			
Anemia	57 (17.2)	30 (18.7)	27 (16.3)
Angina	41 (12.4)	23 (13.7)	18 (10.8)
Heart Failure	31 (9.3)	16 (9.6)	15 (9.0)
Prior Pneumonia	159 (47.9)	83 (50.0)	76 (45.8)
Charlson Score, mean [sd]	5.4 [2.0]	5.5 [2.0]	5.2 [1.8]
COPD Severity			
BODE Index, n (%)			
0-2	105 (31.6)	60 (36.1)	45 (27.1)
3-4	143 (43.1)	74 (44.6)	69 (41.6)
5-6	46 (13.9)	12 (7.2)	34 (20.5)
7-10	38 (11.4)	20 (12.1)	18 (10.8)
GOLD Stage, n (%)			
1	20 (6.0)	10 (6.0)	10 (6.0)
2	163 (49.1)	97 (58.4)	66 (39.8)
3	130 (39.2)	54 (32.5)	76 (45.8)
4	19 (5.7)	5 (3.0)	14 (8.4)

ICS = inhaled corticosteroid; sd = standard deviation

e-Table 4: COPD severity groups adapted from the 2011 GOLD strategy

Symptoms	Exacerbation Risk	
	Low-Risk[a] Prior Year: 0 COPD hospitalizations Past 3 months: 0 exacerbations FEV_1: ≥ 50% predicted	High-Risk[b] Prior Year: 1+ COPD hospitalizations Past 3 months: 1+ exacerbations FEV_1: < 50% predicted
mMRC < 2	A	C
mMRC ≥ 2	B	D

[a] all criteria must be met
[b] the presence of any one of these criteria would categorize patients as high-risk
mMRC = Modified Medical Research Council dyspnea score

e-Table 5: Categorization of baseline inhaler regimen based on the 2011 GOLD strategy

2017 GOLD Group	Aligned	Not Aligned	
		Undertreated	Potentially Overtreated
A	SABD only or LABA only or LAMA only	No inhaled therapy or ICS only	SABD+ICS or LAMA+LABA or LABA+ICS or LAMA+ICS or LABA+LAMA+ICS
B	SABD only or LABA only or LAMA only or LABA+LAMA	No inhaled therapy or ICS only	SABD+ICS or LABA+ICS or LAMA+ICS or LAMA+LABA+ICS
C	SABD only or LAMA only or LAMA+ICS or LABA+ICS or LAMA+LABA	No inhaled therapy or ICS only or LABA only	LABA+LAMA+ICS
D	SABD only or LAMA or LAMA+LABA or LABA+ICS or LAMA+ICS or LAMA+LABA+ICS	No inhaled therapy or LABA only or ICS only	N/A

SABD = short-acting bronchodilator (includes short-acting beta agonist and short-acting muscarinic antagonists); LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid

e-Table 6: Relative risk of experiencing time-to-event outcomes by COPD treatment classification, 2011 GOLD strategy

Outcome by Exposure	2011 Group A/B (n = 209)		2011 Group C/D (n = 529)	
	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)
Primary Outcome				
Death/First Hospitalization for COPD[b]				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.84 (0.27 – 2.68)	0.85 (0.27 – 2.69)	0.76 (0.51 – 1.13)	0.83 (0.57 – 1.21)
Overtreated	1.45 (0.73 – 2.87)	1.34 (0.64 – 2.80)	0.77 (0.52 – 1.16)	1.00 (0.61 – 1.64)
Secondary Outcomes				
Death[b]				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.72 (0.12 – 4.43)	0.71 (0.12 – 4.15)	0.80 (0.37 – 1.72)	0.84 (0.41 – 1.74)
Overtreated	1.24 (0.53 – 2.90)	1.52 (0.66 – 3.52)	0.44 (0.23 – 0.83)	1.06 (0.45 – 2.50)
First Hospitalization for COPD[c]				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.85 (0.27 – 2.73)	0.87 (0.26 – 2.85)	0.69 (0.40 – 1.17)	0.72 (0.41 – 1.26)
Overtreated	1.76 (0.75 – 4.13)	1.41 (0.58 – 3.43)	0.84 (0.54 – 1.33)	0.99 (0.59 – 1.66)
First COPD Exacerbation[d]				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.94 (0.28 – 3.15)	0.81 (0.23 – 2.84)	0.73 (0.53 – 1.01)	0.80 (0.58 – 1.10)
Overtreated	2.09 (1.41 – 3.10)	1.92 (1.28 – 2.87)	1.26 (0.97 – 1.62)	1.47 (1.10 – 1.97)

[a] Cox proportional-hazard models adjusted for baseline age, sex, Charlson score, smoking status, FEV1 percent predicted, and number of all-cause hospitalizations in year before randomization, stratified by BODE Index

[b] Includes all 738 patients enrolled in LOTT

[c] Excludes patients who died prior to experiencing an initial COPD-related hospitalization (n=43)

[d] Excludes patients who died prior to experiencing an initial COPD exacerbation (n=39)

e-Table 7: Relative risk of experiencing time-to-event outcomes by time-varying COPD treatment classification

Outcome by Exposure	2017 Group A/B		2017 Group C/D	
	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)
Primary Outcome				
Death/First Hospitalization for COPD[b]				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.73 (0.39 – 1.37)	0.79 (0.51 – 1.25)	0.97 (0.64 – 1.47)	0.94 (0.72 – 1.22)
Overtreated	1.10 (0.74 – 1.62)	1.02 (0.70 – 1.48)	0.59 (0.28 – 1.26)	0.72 (0.39 – 1.33)
Secondary Outcomes				
Death[b]				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.65 (0.35 – 1.20)	0.56 (0.29 – 1.11)	1.43 (0.55 – 3.74)	1.53 (0.63 – 3.72)
Overtreated	0.69 (0.46 – 1.05)	0.59 (0.39 – 0.90)	0.31 (0.10 – 0.95)	0.48 (0.06 – 3.72)
First Hospitalization for COPD[c]				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.95 (0.40 – 2.28)	0.99 (0.57 – 1.70)	0.89 (0.56 – 1.41)	1.03 (0.65 – 1.62)
Overtreated	1.52 (0.90 – 2.56)	1.33 (0.84 – 2.11)	0.55 (0.21 – 1.49)	0.66 (0.30 – 1.45)
First COPD Exacerbation[d]				
Aligned	Referent	Referent	Referent	Referent
Undertreated	0.84 (0.45 – 1.49)	0.88 (0.53 – 1.48)	1.02 (0.49 – 2.11)	1.01 (0.37 – 2.80)
Overtreated	1.59 (1.12 – 2.25)	1.41 (1.06 – 1.87)	1.36 (0.96 – 1.92)	1.26 (0.82 – 1.94)

[a] Cox proportional-hazard models adjusted for baseline gender, age, Charlson score, smoking status, and number of all-cause hospitalizations in year before randomization, stratified by baseline GOLD stage and BODE Index. Patient reported inhaler regimens were ascertained at 12-month intervals and exposure status (aligned, undertreated, overtreated) was adjusted accordingly. Patient COPD severity status (GOLD groups) was ascertained at baseline only as the annual incidence of inpatient and outpatient respiratory exacerbations was not adjudicated by the original LOTT investigators. While we could have independently adjudicated the annual incidence of COPD exacerbations during follow-up, this would have resulted in discrepancies in the cumulative number of COPD exacerbations.

[b] Includes all 738 patients enrolled in LOTT

[c] Excluded patients who died prior to experiencing an initial COPD-related hospitalization (n=43)

[d] Excluded patients who died prior to experiencing an initial COPD exacerbation (n=39)

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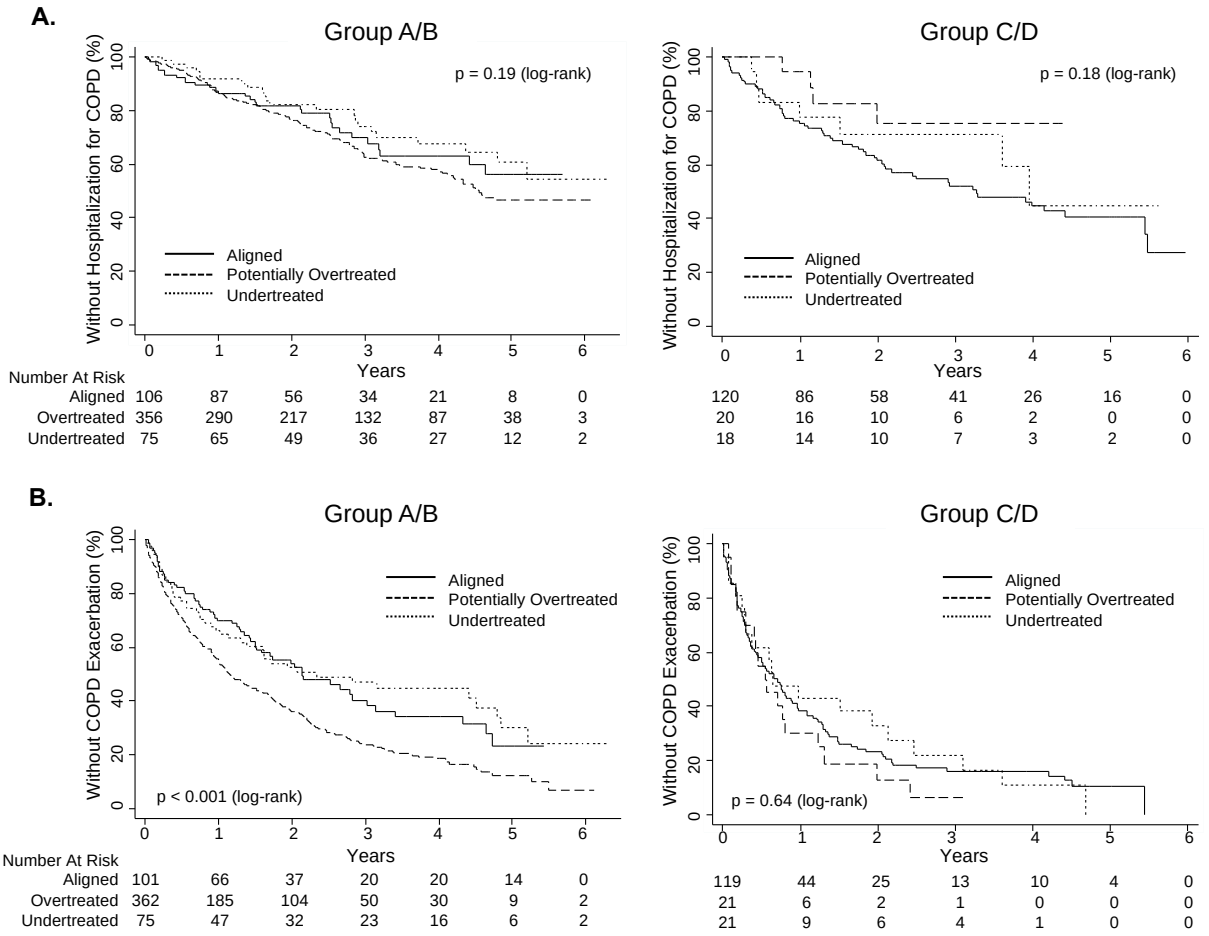
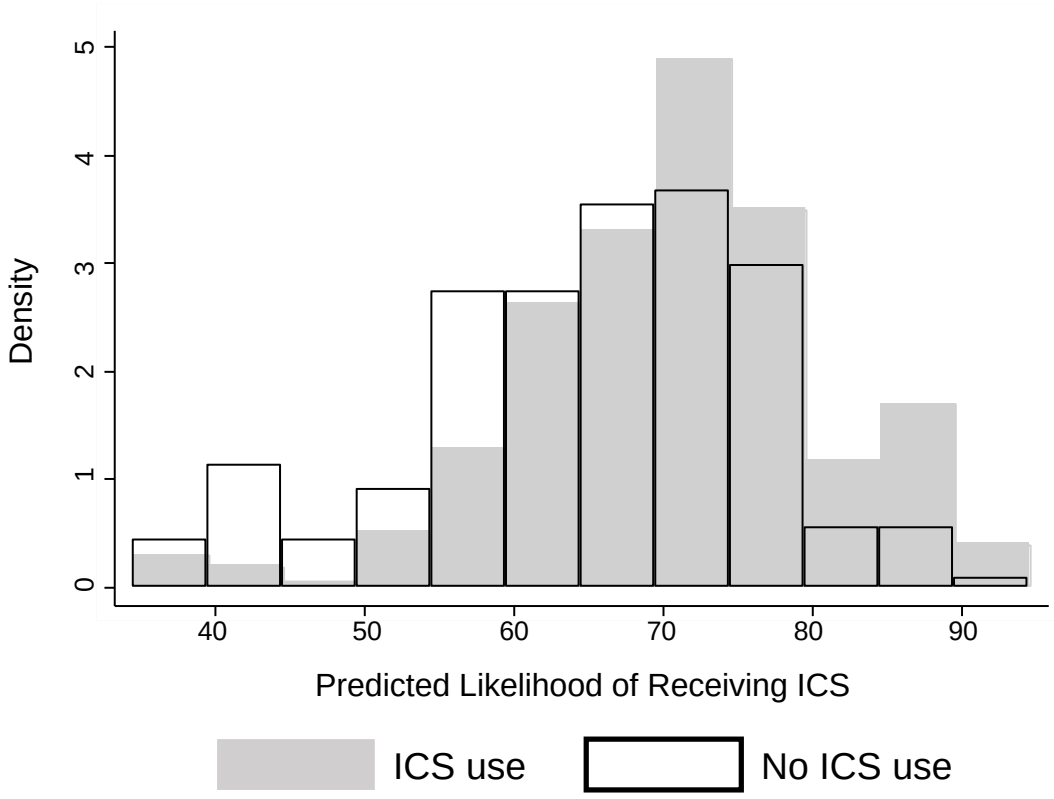
e-Figure 1: Kaplan-Meier analyses for COPD exacerbations by COPD treatment classification

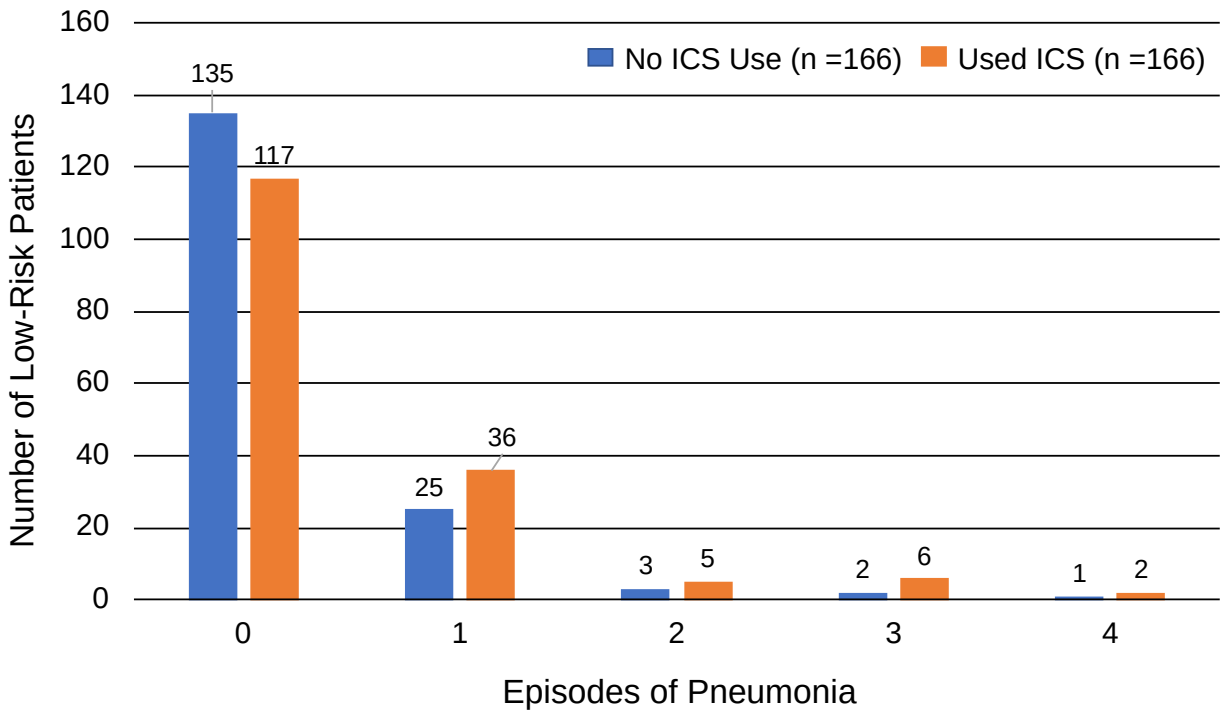


Panel A shows the time-to-event analysis for first COPD-related hospitalization, stratified by predicted exacerbation risk after excluding 43 patients who died without experiencing the outcome (n=695); median follow-up 2.31 yrs. Data for patients who did not have a first hospitalization for COPD were censored at the time of their last interview. A total of 186 patients (34.6%) in group A/B and 71 patients (44.9%) in group C/D experienced the outcome. Panel B shows the time-to-event analysis for first COPD exacerbation, stratified by exacerbation risk after excluding 39 patients who died without experiencing an exacerbation (n=699); median follow-up 1.05 yrs. Data for patients who did not have an initial COPD exacerbation were censored at the time of their last interview. A total of 374 patients (69.4%) in group A/B and 139 patients (85.8%) in group C/D had at least one COPD exacerbation. P values were generated from log-rank tests.

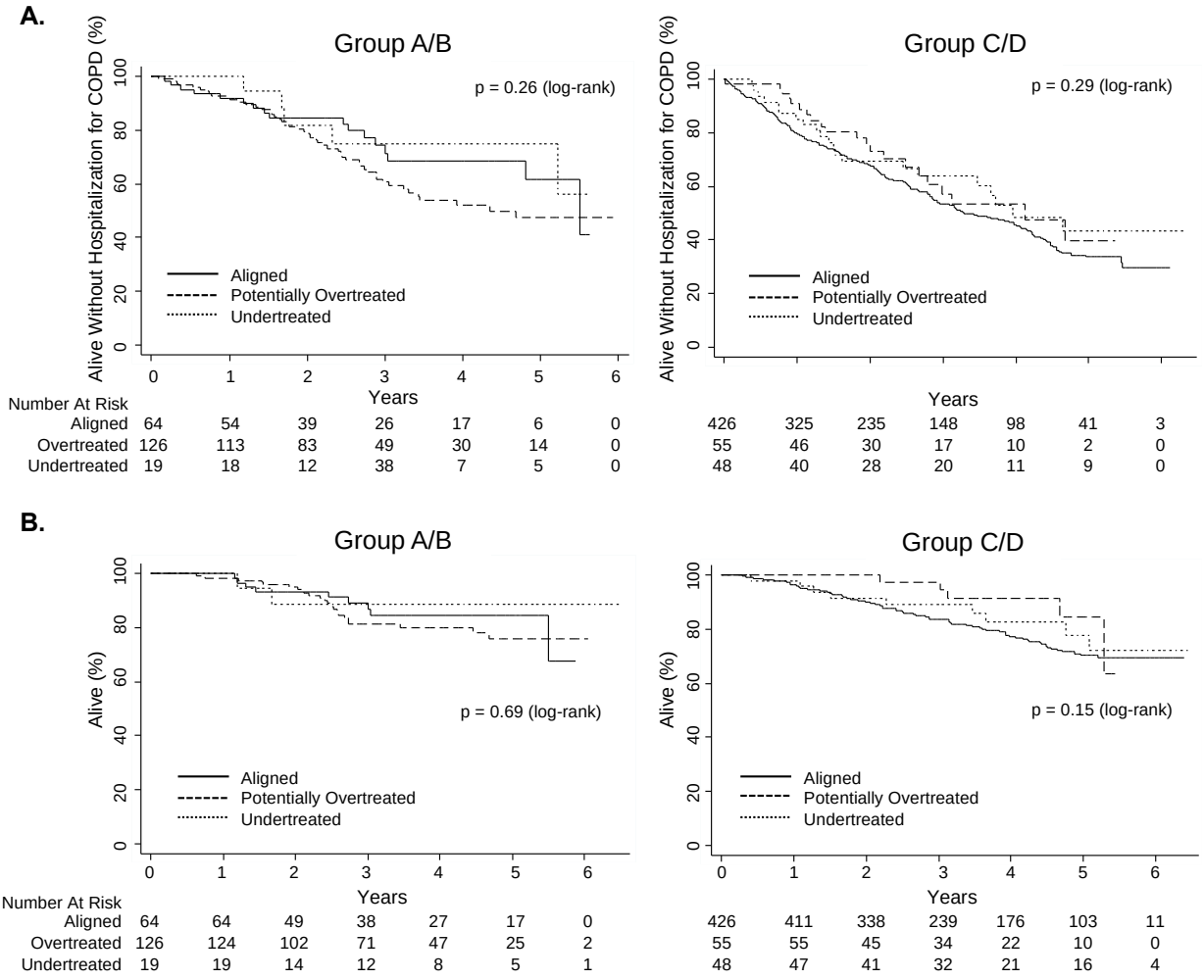
e-Figure 2: Histogram of the predicted likelihood of receiving ICS by reported ICS use



e-Figure 3: Episodes of pneumonia among group A/B patients, by inhaled corticosteroid use

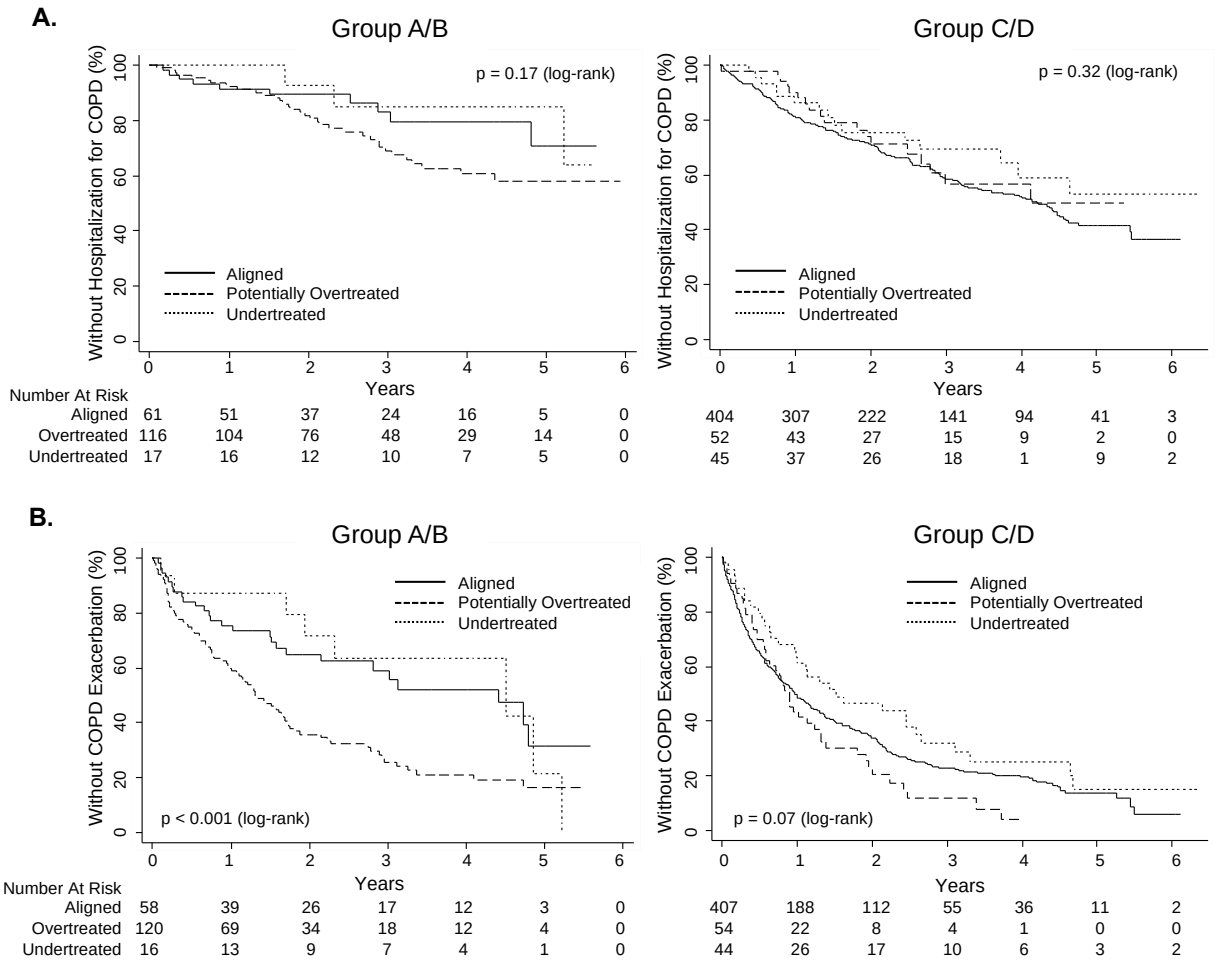


e-Figure 4: Kaplan-Meier analyses for the primary composite outcome and death by COPD treatment classification, 2011 GOLD strategy



Panel A shows the time-to-event analysis for death or first COPD-related hospitalization, stratified by exacerbation risk (n=738); median follow-up 2.29 yrs. Data for patients who neither died nor had a first hospitalization for COPD were censored at the time of their last interview. A total of 71 patients (34.0%) in group A/B and 261 patients (49.3%) in group C/D experienced the composite outcome. Panel B shows the time-to-event analysis for death, stratified by exacerbation risk (n=738); median follow-up 3.46 yrs. Data for patients who were alive as of August 31st, 2015 were censored at the time of their last interview. A total of 33 patients (15.8%) in group A/B and 106 patients (20.0%) in group C/D died. P values were generated from log-rank tests.

e-Figure 5: Kaplan-Meier analyses for COPD exacerbations by COPD treatment classification, 2011 GOLD strategy



Panel A shows the time-to-event analysis for first COPD-related hospitalization, stratified by exacerbation risk after excluding 43 patients who died without experiencing hospitalization (n=695); median follow-up 2.31 yrs. Data for patients who did not have a first hospitalization for COPD were censored at the time of their last interview. A total of 48 patients (24.7%) in group A/B and 209 patients (41.7%) in group C/D experienced the outcome. Panel B shows the time-to-event analysis for first COPD exacerbation, stratified by exacerbation risk after excluding 39 patients who died without experiencing an exacerbation (n=699); median follow-up 1.05 yrs. Data for patients who did not have an initial COPD exacerbation were censored at the time of their last interview. A total of 121 patients (62.1%) in group A/B and 392 patients (77.5%) in group C/D had at least one COPD exacerbation. P values were generated from log-rank tests.

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