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# Chronic Obstructive Pulmonary Disease is Not Associated with In-Hospital Mortality in COVID-19: An Observational Cohort Analysis

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**Background:** Chronic obstructive pulmonary disease (COPD) is associated with worsened outcomes in COVID-19 (coronavirus disease 2019). However, data remain fraught with heterogeneity and bias from comorbid conditions. Additionally, data on the impact of COPD-specific factors, such as pre-hospital medications and pulmonologist involvement, remain sparse.

**Objective:** We report a single-center analysis of COPD patients hospitalized with COVID-19 compared to those without COPD. Primary outcomes include ICU admission, mechanical ventilation, and in-hospital mortality.

**Methods:** We evaluated all patients  $\geq 40$  years admitted with PCR-confirmed COVID-19 between February 2020 and February 2021. COPD was defined by documented ICD-10 diagnosis of COPD, confirmed smoking history, and active bronchodilator use. We compared outcomes between COPD patients and the remainder of the COVID-19 cohort. Multivariable analyses were adjusted for age, sex, smoking status, and comorbid conditions.

**Results:** Of 1537 hospitalized COVID-19 patients, 122 (7.9%) carried a diagnosis of COPD. The COPD cohort was older ( $74 \pm 13$  vs  $66 \pm 15$  years,  $P < 0.001$ ) and more often former smokers ( $P < 0.001$ ). Comorbid conditions including diabetes, cardiovascular disease, and kidney disease were more prevalent in the COPD group ( $P < 0.001$ ). After adjusting for comorbid conditions, the COPD cohort had higher severity scores and trended towards fewer hospital-free days. Among patients with COPD, pre-hospital use of aspirin was associated with decreased ICU admissions (aHR 0.56,  $P = 0.049$ ) and mechanical ventilation (aHR 0.25,  $P = 0.008$ ), while LAMAs (long-acting muscarinic antagonists) were associated with decreased in-hospital mortality (aHR 0.34,  $P = 0.047$ ). Involvement of pulmonology in pre-hospital management of COPD was not found to significantly affect outcomes.

**Conclusion:** When corrected for comorbid illnesses, COPD was associated with more severe disease but not with increased ICU admission, mechanical ventilation, or in-hospital mortality rates. Among COPD patients, prehospital treatment with aspirin and COPD-directed therapies were associated with improved outcomes.

**Keywords:** COVID-19, COPD, survival, critical illness, ARDS

## Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 90 million Americans, resulting in over one million deaths in the United States since the beginning of 2020.<sup>1</sup> Although mortality rates for COVID-19 have been trending down in the United States concordant with increased vaccination rates, new treatment options, and improved clinical understanding of COVID-19,<sup>2-4</sup> at the time of writing, intensive care units (ICUs) worldwide remain congested with patients with severe COVID-19.<sup>5,6</sup>

Researchers have identified a multitude of risk factors associated with severe COVID-19. Congestive heart failure, diabetes, and chronic pulmonary conditions are strongly correlated with increased in-hospital mortality in COVID-19 patients,<sup>7–9</sup> while behavioral risk factors such as previous tobacco use and substance use disorder are linked to worse clinical trajectory.<sup>10,11</sup> It stands to reason, then, that chronic obstructive pulmonary disease (COPD), a chronic pulmonary condition most often caused by longstanding tobacco use, would result in worsened outcomes for hospitalized COVID-19 patients.

Consistent with these findings, published literature suggests a greater risk of adverse outcomes in COVID-19 in patients with concomitant COPD diagnosis.<sup>12–16</sup> However, the majority of these retrospective studies lack individual patient-level data and details on pre-hospital and hospital management.<sup>17</sup> Besides, the need to better understand the association between COPD staging and COVID-19 outcomes, it remains unclear whether adequate outpatient management of COPD prior to the onset of COVID-19 has an impact on clinical outcomes in patients with COPD hospitalized for COVID-related complications. We hypothesized that variations in COPD treatment regimens and objective markers of COPD severity would be associated with differences in outcomes. To this aim, we conducted a retrospective analysis of ever-smokers with formal COPD diagnosis treated with inhaled therapies who were hospitalized with acute COVID-19, focusing on specific endpoints of ICU admission, need for mechanical ventilation, and in-hospital mortality.

## Methods

### Cohort Specification

We compiled a retrospective cohort analysis of 1537 patients admitted for COVID-19 infection to both UCLA Ronald Reagan and UCLA Santa Monica Medical Centers between February 2020 and February 2021. Eligible patients were at least 40 years old with a positive COVID-19 PCR requiring hospitalization at any level of care (non-monitored, monitored, intermediate, or intensive care unit). COPD cohort was defined as having all three of the following: documented International Classification of Diseases (ICD)-10 diagnosis of COPD (ICD-10 code J44.9), self-reported tobacco smoking history, and self-reported outpatient bronchodilator use. Comorbid conditions were reported by a similar methodology using ICD-10 codes ([Supplemental Table 1](#)). All data was prospectively maintained within our institutional registry database and individual chart review of electronic medical record (EMR) was done to complete missing or incomplete data to the extent possible. Outside institution records were reviewed when available via Care Everywhere™ (Epic Systems, Verona, WI) and included if they were more recent than those available in our EMR or relevant to our patient's medical records (eg, non-established UCLA patients with no prior records at our institution). Each COPD diagnosis was independently reviewed prior to analysis to ensure the above inclusion criteria for COPD categorization were met. Patients were excluded from the COPD group for misdiagnosis of COPD (eg, asthma) or history of lung transplantation.

### Outcome Measures

Primary outcomes were ICU admission, need for mechanical ventilation, and in-hospital mortality. Secondary outcomes included supplemental oxygen requirement, length of hospitalization, and NIH (National Institutes of Health) severity scores (defined below).

Supplemental oxygen use was defined by any supplementation of oxygen above ambient atmosphere. Mechanical ventilation was defined by invasive ventilation requiring endotracheal intubation, whereas non-invasive mechanical ventilation was defined by the use of high-flow nasal-cannula systems or positive airway pressure (PAP) ventilation with bi-level or continuous PAP. Ordinal scores from the NIH Severity Scale<sup>18</sup> were defined with scores corresponding to the level of COVID severity as referenced in [Supplemental Table 2](#).

### Covariate Specification

Available data on COPD treatment was collected for patients within the COPD cohort. We tabulated the prescription of long-acting muscarinic antagonists (LAMA), long-acting beta agonists (LABA), and inhaled corticosteroids (ICS) prior to hospital admission. We additionally collected data on the pre-admission prescription of daily aspirin (ASA) and oral beta-blockers, as these two groups of medications have been associated with improving outcomes in COPD.<sup>19,20</sup> Most

recent pulmonary function testing (PFT), collected if available, included forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), and diffusing lung capacity for carbon monoxide (DLCO). We also reviewed charts for evidence of prior COPD exacerbations that necessitated a prescription of a limited course of oral corticosteroids with or without antibiotics in our COPD cohort. Lastly, we recorded whether patients were being managed by a pulmonologist for their COPD rather than a general practitioner. Prospective data were exported to a REDCap (Vanderbilt University, Nashville, TN) database daily, with “admission” values considered to be those collected at intake (or within 24 hours of hospital admission if intake values were not available).

COVID-19 specific interventions and management were conducted by individual treatment teams without input from study personnel and in accordance with best practice guidelines available at the time of admission and treatment. This study was approved by the University of California, Los Angeles institutional review board (IRB 20–200473), which provided a waiver of consent for all admitted patients with a COVID diagnosis to prevent confounding. Collected patient records were de-identified to protect patient confidentiality and kept in an encrypted institution-provided cloud-based database.

## Statistical Analysis

Preliminary comparisons of baseline characteristics between COPD and non-COPD groups were carried out using Welch’s *t*-test for continuous variables, chi-square test for categorical variables and Mood’s median test for non-normally distributed laboratory test values. Time dependent outcomes were compared by COPD status using the Gray’s test. NIH severity score and length of stay were compared between groups using the Wilcoxon rank sum test. Hospital-free days, as defined by the length of time a patient is alive and not in the hospital within a study window of 28 days, was compared using linear regression models.

The Fine and Gray competing risk regression model was used to evaluate time-dependent outcomes by COPD status before and after adjusting for covariates and results were summarized as unadjusted and adjusted hazard ratios (HR). The following pre-specified covariates were adjusted for in the models: age, sex, tobacco smoking status, history of chronic kidney disease, congestive heart failure, and diabetes. Competing risk models for ICU admission and mechanical ventilation accounted for competing events including in-hospital death and hospital discharge. Competing risk model for in-hospital death was adjusted for hospital discharge as a competing event; meanwhile, the competing model for hospital discharge was adjusted for in-hospital death. Patients who were transferred to another hospital were treated as censored observations. The nominal logistic model was used to evaluate the relationship between COPD status and NIH severity score before and after adjusting for the same covariates as above. We used the nominal logistic model rather than the ordinal logistic model after verifying that assumptions of the ordinal model were not met and the nominal model was, therefore, more appropriate in this data. Results were reported as unadjusted and adjusted odds ratios (OR) using the lowest NIH category as the reference group for computing the odds ratios.

Subset analyses were performed among patients with COPD to assess the relationship between pre-hospitalization COPD treatment variables and specific clinical outcomes. Time dependent outcomes were analyzed using the Fine and Gray competing risk model similarly as above. The NIH severity score, an ordinal outcome, was analyzed using the ordinal logistic model after verifying the proportional odds assumption. For this model, values of the dependent variable were cumulated over lower ordered categories and results were reported as cumulative odds ratios (OR). All models were adjusted for the same covariates as above using the propensity score method. Correlations between pulmonary function tests versus NIH severity score and LOS were assessed using Spearman correlation. The relationship between pulmonary function tests and time-dependent outcomes was performed using similar methods as above. *P*-value <0.05 were considered statistically significant.

## Results

### Baseline Demographics and Inflammation in COPD vs Non-COPD Patients

Of the 1537 hospitalized COVID-19 patients in our dataset, 122 (7.9%) had a concomitant diagnosis of COPD as defined by our inclusion criteria (Table 1). COPD patients were significantly older ( $74 \pm 13$  vs  $6 \pm 15$  years,  $P < 0.001$ ) and more likely to be active smokers (10% vs 4%,  $P = 0.002$ ) or former tobacco users (90.2% vs 24.3%,  $P < 0.001$ ) compared to their non-COPD counterparts. Comorbidities including diabetes, cardiovascular diseases, and chronic kidney disease

**Table 1** Baseline Demographics, Comorbidities and Outcomes in COPD vs Non-COPD Patients

	<b>Non-COPD (n = 1415)</b>	<b>COPD (n = 122)</b>	<b>P value</b>
<b>Demographics</b>			
Age, mean (SD) <sup>a</sup>	66.4 (14.7)	74.2 (12.6)	<0.001
Male, % <sup>b</sup>	56.4%	59%	0.575
BMI, mean (SD) <sup>a</sup>	28.2 (6.8)	28.6 (8.0)	0.619
Active tobacco smoking, % <sup>b</sup>	3.9%	10%	0.002
Former tobacco smoking, % <sup>b</sup>	24.3%	90.2%	<0.001
<b>Prior Comorbidities<sup>b</sup></b>			
Diabetes, %	20.8%	40%	<0.001
Coronary artery disease, %	13.1%	30%	<0.001
Heart failure, %	18.8%	48%	<0.001
Chronic kidney disease, %	27.4%	49%	<0.001
Chronic pulmonary condition, %	21.4%	100%	<0.001
Liver disease, %	5.9%	5%	0.667
Cerebrovascular disease, %	18.2%	35%	<0.001
Peripheral vascular disease, %	18.3%	47%	<0.001
<b>Admission Inflammatory Markers</b>			
White blood cell count (×10 <sup>9</sup> cells/L), mean (SD) <sup>a</sup>	7.54 (4.87)	6.30 (3.72)	0.001
Neutrophil count (×10 <sup>9</sup> cells/L), mean (SD) <sup>a</sup>	5.88 (4.48)	4.78 (3.43)	0.001
Lymphocyte count (×10 <sup>9</sup> cells/L), mean (SD) <sup>a</sup>	1.01 (1.27)	0.96 (0.80)	0.539
Monocyte count (×10 <sup>9</sup> cells/L), mean (SD) <sup>a</sup>	0.37 (1.01)	0.33 (0.96)	0.781
Neutrophil-Lymphocyte ratio, mean (SD) <sup>a</sup>	8.62 (10.88)	8.08 (8.96)	0.534
C-reactive protein (mg/L), mean (SD) <sup>a</sup>	8.59 (7.07)	7.10 (6.23)	0.020
Lactate (mg/dL), mean (SD) <sup>a</sup>	17.23 (15.30)	16.55 (13.25)	0.664
IL-6 (pg/mL), median (IQR) <sup>c</sup>	7.0 (16.0)	5.5 (11.8)	0.675
Procalcitonin (ng/mL), median (IQR) <sup>c</sup>	0.16 (0.41)	0.14 (0.34)	0.226
D-dimer (ng/mL), median (IQR) <sup>c</sup>	1090 (1571)	1115 (1640)	0.233
<b>Outcomes</b>			
Oxygen therapy, % <sup>b</sup>	86.1	95.9	0.002
ICU admission, % <sup>b</sup>	31.6	35.2	0.691
Mechanical ventilation, % <sup>b</sup>	17.0	19.7	0.446
In-hospital mortality, % <sup>b</sup>	13.9	18.9	0.048
NIH Severity Score, n (%) <sup>c</sup>			<0.001
4	193 (13.6%)	4 (3.3%)	
5	30 (2.1%)	5 (4.1%)	
6	889 (62.8%)	77 (63.6%)	
7	135 (9.5%)	12 (9.9%)	
8	168 (11.9%)	23 (19.0%)	
Length of stay (days), mean (SD) <sup>d</sup>	10.0 (10.9)	13.1 (12.4)	0.009
<b>Treatments<sup>b</sup></b>			
Remdesivir, %	57.7	66.4	0.205
Dexamethasone, %	51.0	60.7	0.150
Systemic steroids, %	59.4	69.7	0.158
Antibacterials, %	68.1	74.6	0.322

**Notes:** <sup>a</sup>Welch's Two Sample t-Test; <sup>b</sup>Chi-squared Test of Independence; <sup>c</sup>Mann-Whitney U-Test; <sup>d</sup>Wilcoxon Rank Sum Test.

**Abbreviations:** BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NIH, National Institutes of Health.

were more prevalent in COPD patients, while differences in liver disease were not statistically significant. No appreciable differences in BMI (body mass index) or sex were noted between the groups, and both groups also had similar inflammatory profiles at hospital admission.

## COPD Status and Clinical Outcomes

Preliminary unadjusted analysis demonstrated statistically higher rates of in-hospital mortality among COPD patients (Table 1). ICU admission and mechanical ventilation rates were also increased among patients with COPD but did not reach statistical significance. COPD patients had greater utilization rates for oxygen therapy during hospitalization (95.9% vs 86.1%,  $P = 0.002$ ). These findings are reflected by increased composite NIH severity scores in COPD patients compared to non-COPD patients ( $P = 0.009$ ). Secondary metrics for COVID severity including length of hospitalization were also notably higher in patients with COPD (13 vs 10 days,  $P = 0.009$ ). Both groups were just as likely to receive COVID-specific treatments such as remdesivir, dexamethasone, and other systemic steroids.

After adjusting for covariates including age, sex, smoking status, and comorbidities associated with poor clinical outcomes in COVID-19 (chronic kidney disease, congestive heart failure, and diabetes),<sup>7,8,21</sup> patients with COPD maintained higher NIH severity scores and had fewer hospital-free days (Table 2). Despite reaching statistical significance, the effective differences between the two groups were notably smaller after adjusting for covariates.

Primary outcomes (ICU admission, mechanical ventilation, and in-hospital mortality) were also examined after accounting for competing risks including hospital transfers and discharge (Table 3). Patients with COPD were more likely to experience in-hospital mortality (HR 1.67 [1.09, 2.55],  $P = 0.018$ ) while hazards for ICU admission and mechanical ventilation were comparable to patients without COPD. However, there was no statistical difference in all three outcomes after adjusting for covariates on top of competing risk analysis. The proportion of censored patients in competing risk analysis fluctuated between 12.93% and 29.51% with in-hospital death having the most censored patients in both patient groups (Supplemental Table 3).

## Pre-Hospitalization COPD Management and COVID-19 Outcomes

The effects of pre-admission COPD management, including both prescribed medications and health system interventions, on COVID outcomes were evaluated among COPD patients in Table 3. Chart review showed that neither management by a pulmonologist nor previous history of COPD exacerbation was associated with any difference in primary outcomes during the index hospitalization (Supplemental Table 4). However, patients prescribed aspirin (ASA) prior to hospitalization had lower hazards of ICU admission (aHR 0.56,  $P = 0.049$ ) and mechanical ventilation (aHR 0.25,  $P = 0.008$ ) after propensity score matching (Table 3). Long-acting beta agonists (LABAs) were also associated with decreased hazards of mechanical ventilation (aHR 0.38,  $P = 0.050$ ) and lower NIH severity scores (aOR 0.45,  $P = 0.040$ ), while use of long-acting muscarinic

**Table 2** Assessment of COPD Impact on COVID Severity

	Odds Ratio	95% Confidence Interval	P value
<b>Unadjusted<sup>a</sup></b>			
NIH Severity Score COPD vs non-COPD			
Score 5 versus 4	8.04	2.04–31.64	0.003
Score 6 versus 4	4.18	1.51–11.56	0.006
Score 7 versus 4	4.29	1.35–13.58	0.013
Score 8 versus 4	6.61	2.24–19.49	0.001
<b>Adjusted<sup>a*</sup></b>			
NIH Severity Score (OR)			
Score 5 versus 4	5.89	1.30–26.67	0.021
Score 6 versus 4	3.71	1.29–10.71	0.015
Score 7 versus 4	4.90	1.43–16.80	0.011
Score 8 versus 4	3.43	1.09–10.80	0.034
	Non-COPD Mean (SE)	COPD Mean (SE)	P value
Adjusted Hospital-Free Days <sup>b*</sup>	16.9 (0.3)	14.8 (1.1)	0.058

**Notes:** <sup>a</sup>Nominal logistic model, <sup>b</sup>Linear regression model with bootstrapping, \*Adjusted for Age, Sex, Smoking Status, and Comorbidities (chronic kidney disease (CKD), congestive heart Failure (CHF), diabetes).

**Table 3** Primary Outcomes and Medication Effect Among Patients with COPD

	n		ICU Admission		Mechanical Ventilation		In-Hospital Death	
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Unadjusted <sup>a</sup>								
COPD patients	122		1.12 (0.84, 1.50)	0.428	1.40 (0.90, 2.19)	0.139	1.67 (1.09, 2.55)	0.018
Adjusted <sup>a*</sup>								
COPD patients	122		1.13 (0.81, 1.56)	0.473	1.28 (0.76, 2.14)	0.354	0.93 (0.57, 1.52)	0.776
	Yes (n)	No (n)	ICU Admission		Mechanical Ventilation		In-Hospital Death	
			aHR (95% CI)	P	aHR (95% CI)	P	aHR (95% CI)	P
Medications <sup>a*</sup>								
ASA	60	62	0.56 (0.32, 1.00)	0.049	0.25 (0.09, 0.70)	0.008	0.87 (0.38, 1.98)	0.731
LABA	51	71	0.60 (0.33, 1.09)	0.093	0.38 (0.15, 1.00)	0.050	0.52 (0.22, 1.21)	0.127
LAMA	44	77	0.55 (0.27, 1.12)	0.099	0.18 (0.04, 0.80)	0.024	0.34 (0.11, 0.99)	0.047
Inhaled Corticosteroid	53	69	0.62 (0.35, 1.13)	0.117	0.51 (0.21, 1.26)	0.145	0.75 (0.34, 1.66)	0.481
	Yes (n)	No (N)	NIH Severity Score		Length of Stay (days), mean (SE)			
			aOR (95% CI) <sup>c</sup>	P	Yes	No	P	
Medications <sup>b*</sup>								
ASA	60	62	0.56 (0.26, 1.21)		0.142	10.6 (1.2)	15.4 (1.9)	0.040
LABA	51	71	0.45 (0.21, 0.97)		0.041	13.8 (2.1)	12.5 (1.4)	0.610
LAMA	44	77	0.33 (0.14, 0.76)		0.009	6.29 (0.11)	6.43 (0.12)	0.137
Inhaled Corticosteroid	53	69	0.65 (0.31, 1.37)		0.254	13.2 (1.78)	13.0 (1.37)	0.915

**Notes:** <sup>a</sup>Fine and Gray Competing Risk Model; <sup>b</sup>Wilcoxon Rank Sum Test; <sup>c</sup>Nominal logistic model. \*Adjusted with Propensity-score Matching. Hazard ratios are compared to null treatment/interventions.

**Abbreviations:** ASA, aspirin; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist.

antagonists (LAMAs) was correlated with less need for mechanical ventilation and lower in-hospital mortality (aHR 0.18,  $P = 0.024$  and aHR 0.34,  $P = 0.047$ , respectively). Only ASA was associated with shorter hospitalizations ( $11 \pm 1$  vs  $15 \pm 2$  days,  $P = 0.040$ ). Inhaled corticosteroid use did not confer any effects on primary or secondary outcomes.

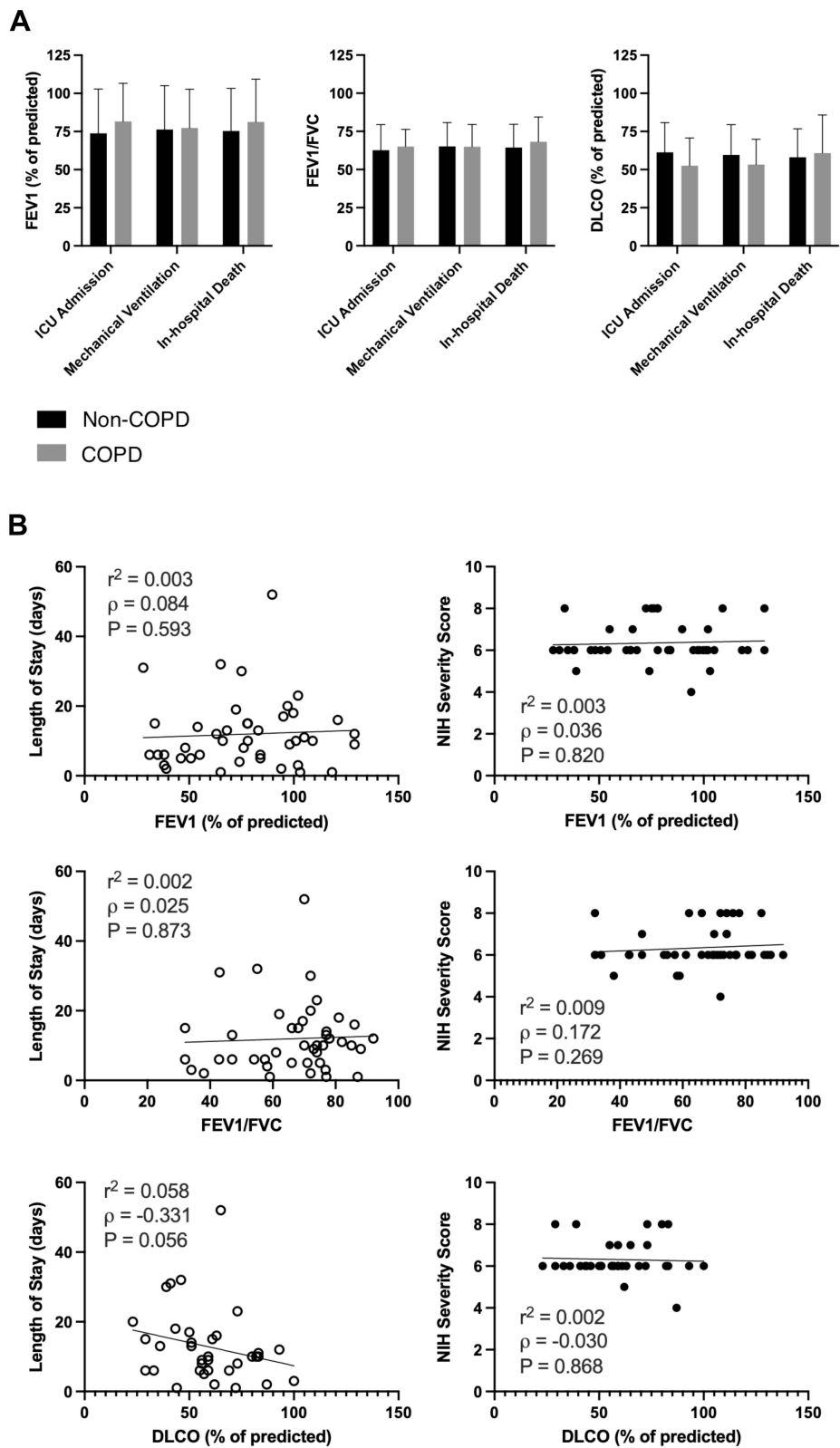
## Pre-Hospitalization PFTs as a Predictor of Outcomes in COPD Patients with COVID-19

Pulmonary function tests (PFTs) were available in a subset of our COPD cohort ( $n = 44$ ; 36.1% of COPD patients). Median time since last known PFT prior to index hospitalization was 1108 days with an inter-quartile range of 1281 days (minimum: 175 days, maximum: 4661 days). In univariable analyses, most recent PFTs obtained prior to hospital admission demonstrated no clear association with COVID outcomes (Figure 1; Supplemental Table 5). No correlation was appreciated between PFT values and NIH severity scores or hospitalization duration.

## Discussion

In our study of hospitalized patients with COVID-19, while associated with higher severity scores and fewer hospital-free days, after adjustments for comorbid conditions, COPD was not associated with drastically worsened outcomes. Additionally, we attempted to identify signals within the COPD cohort predictive of improved outcomes and found that outpatient use of ASA, LAMA, and LABA prior to hospitalization was associated with better outcomes within the COPD cohort. Analyzing a small subset of those with available data, neither PFT values nor prior management by a pulmonologist correlated with specific COVID outcomes. Our study, therefore, adds an additional and more balanced view to the predominantly held position of COPD being an absolute risk factor for poor outcomes in the setting of COVID-19.

SARS-CoV-2 virus has a clear predilection for pulmonary involvement, leading to COVID-19 pneumonia. Given the resulting inflammation and disruption of gas exchange characteristics of the disease, it stands to reason that patients with



**Figure 1** Pulmonary Function Test values and outcomes among COPD group. Outcome measurements for COPD patients with pulmonary function test (PFT) values (FEV1, FEV1/FVC, DLCO). (A) PFTs among COPD patients stratified by outcome status. (B) Spearman correlations between PFTs and length of stay and NIH severity scores.



pulmonary pathology at baseline are at increased risk for more severe disease and worsened clinical course. Furthermore, because the natural progression of COPD involves chronic inflammation and damage to small airways as well as impaired gas exchange from ventilation/perfusion mismatch, one might expect patients with advanced COPD to fare worse with COVID than those with milder disease due to lack of pulmonary reserve. Multiple studies identified COPD as a significant risk factor for more severe disease and even death.<sup>17,22</sup> However, most previous studies do not correct for comorbidities that can worsen COVID outcomes when assessing for associations between COPD and COVID disease severity.<sup>7,8,21</sup> One of the earliest studies to address COPD as a risk factor for severe COVID, Guan et al, reported that COPD patients had higher 30-day risks of invasive ventilation, admission to intensive care unit, or death if hospitalized for COVID-19.<sup>23</sup> While an early landmark publication in the study of COVID-19, it did not correct for the possible confounding of coexisting illnesses that often accompany COPD diagnoses. Given the large patient population included, especially for so early in the pandemic, this often-cited study frequently comprises a large percentage of subsequent COVID meta-analyses.<sup>24,25</sup> As a result, it is possible that the markedly worse outcomes seen in COPD patients in earlier studies may have been over-attributed to COPD itself due to under-recognition of the contribution of associated conditions. Indeed, a long-term national study in South Korea by Jeong et al undertaken concurrently with ours also found COPD to be an independent risk factor for contracting COVID while not increasing risk for disease severity or death, strengthening our findings and highlighting the impact of population-level disease on COVID-related outcomes research.<sup>26</sup> Moreover, our cohort reflects a relatively long period of more experienced COVID-19 management, thus the impact of initial gaps in adequate management and global confusion over effective therapeutics earlier in the pandemic is less evident in comparison to earlier studies.<sup>27</sup> All patients were managed in a large academic center with tightly coordinated management in accordance with the latest evidence-based approach at the time.

Another plausible explanation for the reduced effects of COPD on COVID outcomes in our study may lie in the prevalence of active tobacco smoking within our dataset. Active smoking has been found to upregulate the ACE2 (angiotensin-converting enzyme 2) receptors used for viral entry into the cell. Additional studies have shown increased viral replication in patients who actively smoked, more so than former smokers.<sup>12</sup> Our study population had a relatively small percentage of active tobacco users (<10%) within the COPD cohort, thus further diluting the negative effects of having a concurrent COPD diagnosis and active smoking in COVID patients.

Exciting new research also may further implicate genomic differences in COVID-19 susceptibility throughout different populations. Recent literature suggests polymorphisms of both the ACE and ACE2 genes likely play a significant role in disease severity and mortality.<sup>28,29</sup> Indeed, individual alleles in the ACE gene have even been associated with different risks of severe disease. The II allele, which produces the least amount of ACE in tissue and plasma, is associated with the most severe COVID disease courses, whereas the DD allele, producing the most ACE in tissue and plasma, is the allele most associated with asymptomatic disease.<sup>30</sup> Fließer et al further added to this understanding by demonstrating between decreased soluble ACE levels in COPD, which may inform on the increased severity of disease seen in COPD patients, though, as our results suggest, perhaps not to the level previously believed.<sup>31</sup> While our study design did not allow genomic evaluation, future research may consider correlation of disease severity and genomic analyses.

Further analysis within the cohort of COPD patients yielded several other interesting findings. While COPD severity defined by FEV1% predicted did not appear to influence clinical outcomes, possibly due to the low number of participants with PFTs available, it is interesting to note that we also could not identify any association between the outcomes and specialized pulmonology-based care prior to the admission; having an outpatient pulmonologist was not associated with better outcome, despite having a pulmonologist has previously been shown to affect the optimization of COPD management,<sup>32</sup> though biases inherent to database studies may call this finding into question. On the other hand, after propensity score matching to account for confounders, ASA, LAMA, and LABA medications were each associated with significant improvements in length of stay, ICU admission, mechanical ventilation, and even death. This finding is not altogether surprising as the use of these medications could be associated with several biases based on patient compliance with prescribed medication and better outpatient management in comparison to those without inhalers. On the other hand, limited evidence suggests a true positive effect of the inhaled LAMA/LABA since these medications have been found to decrease viral replication in cultured tracheal and nasopharyngeal tissue.<sup>33</sup> Interestingly, the latter study

also showed decreased viral replication with ICS, although no significant association of ICS therapy with the outcomes was found in our patient population. Lastly, our finding of decreased ICU admission, mechanical ventilation, and length of stay associated with pre-hospital aspirin supports the findings in a recent publication suggesting that early aspirin administration may be associated with improved COVID outcomes.<sup>19</sup> Given the inflammatory and prothrombotic nature of COVID with inflammatory disruption of gas exchange as well as thrombotic disease such as pulmonary embolism, it is not surprising that a medication with both anti-inflammatory and antithrombotic properties such as aspirin could be associated with improved outcomes.

Our study has limitations which are important to be emphasized. As a retrospective analysis of a relatively small number of individuals with COPD from a single center, our study is prone to inherent biases and unmeasured confounding that could influence our overall findings. Complete medical and medication history collection has been based on standardized care and may be prone to certain inaccuracies, especially considering the rapidly evolving landscape of COVID-19 management approaches over the period studied. Only a third of the identified cohort had documented PFTs in our database prior to the hospitalization. Missing PFT values are likely a function worse outpatient management due to healthcare disparities and are, therefore, likely not random and cannot be rectified with imputation. COPD diagnosis was also based on ICD-10 coding with its inherent flaws of underreporting COPD diagnoses.<sup>34</sup> As a result, a documented history of ever tobacco smoking and use of bronchodilators were added as inclusion criteria to reduce the effect of ICD-10 coding inaccuracies. It is also possible that some individuals with COPD might have been clustered in the “non-COPD” cohort. To account for this, data was prospectively maintained as completely as possible over the study period and only augmented as necessary from the EMR. Additionally, independent investigators reviewed the diagnoses of all patients within the COPD cohort to ensure accuracy. While treatment and management were guided by standard practice at the time, these practices were changing at times daily. The rise of SARS-CoV-2 variants also presents new variables as our study interval likely only captured the Alpha variant. Major variants including Delta and Omicron were not assessed in our study pool as the two variants were not endemic in the United States until March 2021 and December 2021, respectively.<sup>35</sup> As a result, COVID-19 specific treatments varied across time and are not able to be standardized across study groups, adding a possible confounding element for which we are unable to account.

Nevertheless, several strengths should be emphasized. This report is based on data from a large and well-characterized database from a large quaternary academic center from the early phase of the COVID-19 pandemic. Medical and supportive management were mandated to follow current CDC guidelines, and our centers did not have any major shortages or system limitations that could impact outcomes. In addition to comparing the outcomes of COPD patients to those without this disease, this study evaluated the association between COPD characteristics (including PFTs, past COPD exacerbations, medications, and provider history) and COVID-19 outcomes. As opposed to multiple other studies identifying COPD based on ICD codes, a method which carries risk of significant inaccuracy,<sup>36</sup> we applied additional criteria which included smoking history and use of inhaler therapies, thus maximizing the specificity and allowing for the study to better understand the disease course in those who are more likely to be clinically diagnosed and managed for COPD.

## Conclusion

Patients with COPD hospitalized for acute COVID-19 at a major medical center had higher NIH severity scores and longer hospital stays in comparison to those without COPD after adjusting for age and comorbidities. However, there was no difference in mortality or rates of ICU admission and mechanical ventilation. While there was no association between pulmonary function and major outcomes, long-acting muscarinic agonists and aspirin were associated with lower rates of mechanical ventilation. Our findings highlight the complex relationship between SARS-CoV2 infection, underlying patient characteristics and COPD. With continuing waves of new variants and viral mutations, the better understanding we have of COVID-19 and its complex interaction with human diseases, the better we can prepare ourselves to care for our patients and loved ones.

## Disclaimers

Drs. Buhr and Fulcher are employed by the Veterans Health Administration. The views in this manuscript do not necessarily represent those of the Department of Veterans Affairs or US Government.

## Ethics Approvals

This study was reviewed and approved by the UCLA Institutional Review Board (20-200473) on June 12, 2020.

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## Disclosure

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