

# Letters

## RESEARCH LETTER

### Association of Smoking and Cumulative Pack-Year Exposure With COVID-19 Outcomes in the Cleveland Clinic COVID-19 Registry

There is limited and contradictory evidence on the association of smoking status with adverse outcomes of severe acute respiratory syndrome coronavirus 2 infection.<sup>1-3</sup> Furthermore, current smoking status does not encompass the cumulative effect of smoking. To our knowledge, no studies have assessed the cumulative effect of smoking over time, as measured by pack-years, though a single study of coronavirus disease 2019 (COVID-19) in a small cohort of 102 patients with lung cancer found that the patients with severe outcomes had a higher average pack-year history (30 vs 20 years).<sup>4</sup> We hypothesize

that there is an adverse association of cumulative smoking exposure, as measured by pack-years, with outcomes of patients with COVID-19.

**Methods |** The Cleveland Clinic initiated a COVID-19 registry starting on March 8, 2020, that includes all patients tested for COVID-19 within the Cleveland Clinic Health system in Ohio and Florida. Basic demographic information was collected during testing, including age, height, weight, self-reported gender, self-reported race, and select comorbidities. Additional data on comorbidities, medications, and outcomes were extracted from patient electronic medical records.<sup>5</sup> The Cleveland Clinic Institutional Review Board approved this study and waived the need for patient informed consent owing to use of deidentified database information on study participants.

**Table 1. Demographics of Patients Who Tested Positive for COVID-19 Within the Cleveland Clinic Health System**

Characteristic	Smokers, No. (%)				P value	
	Never (n = 6020)	0-10 Pack-years (n = 341)	10-30 Pack-years (n = 400)	>30 Pack-years (n = 341)		
Age, mean (SD), y	47.8 (19.3)	56.5 (17.2)	65.2 (13.8)	71.0 (11.0)	<.001	
Female	3683 (61.2)	191 (56.0)	212 (53.0)	145 (42.5)	<.001	
Race						
Black	1911 (31.7)	120 (35.2)	100 (25.0)	78 (22.9)	<.001	
White	3370 (56.0)	201 (58.9)	277 (69.3)	245 (71.9)		
Other	424 (7.0)	8 (2.4)	12 (3.0)	7 (2.0)		
BMI score						
Underweight (<18.5)	41 (0.7)	2 (0.6)	11 (2.8)	3 (0.9)	<.001	
Normal (18.5-24.9)	682 (11.3)	35 (10.3)	48 (12.0)	66 (19.4)		
Overweight (25.0-29.9)	1081 (18.0)	54 (15.8)	92 (23.0)	85 (24.9)		
Obese (>30.0)	1632 (27.1)	125 (36.7)	132 (33.0)	125 (36.7)		
Pack-years, mean (SD)	0 <sup>a</sup>	5.3 (3.4)	20.8 (5.8)	55.1 (24.9)	<.001	
Current smokers	0 <sup>a</sup>	49 (14.4)	67 (16.8)	56 (16.4)	.64	
Received flu shot this year	1742 (45.6)	220 (64.5)	253 (63.3)	259 (76.0)	<.001	
Comorbidity						
COPD/emphysema	156 (2.6)	32 (9.4)	91 (22.8)	161 (47.2)	<.001	
Asthma	946 (15.7)	85 (24.9)	95 (23.8)	78 (22.9)		
Diabetes	1006 (16.7)	89 (26.1)	134 (33.5)	147 (43.1)		
Hypertension	2263 (37.6)	196 (57.5)	281 (70.3)	288 (85.5)		
Coronary artery disease	423 (7.0)	48 (14.1)	106 (26.5)	147 (43.1)		
Heart failure	348 (5.8)	32 (9.4)	76 (19.0)	110 (32.3)		
Cancer (historical or current)	583 (9.7)	63 (18.5)	105 (26.3)	105 (30.8)		
Medications <sup>b</sup>						
Inhaled or oral corticosteroids	583 (9.7)	58 (17.0)	60 (15.0)	66 (19.4)		.62
NSAIDs	1205 (20.0)	100 (29.3)	117 (29.3)	105 (30.8)	.98	
ACE inhibitor	441 (7.3)	53 (15.5)	61 (15.3)	51 (15.0)	.99	
ARB	350 (5.8)	34 (10.0)	46 (11.5)	48 (14.1)	.56	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019 NSAID, nonsteroidal anti-inflammatory drug.

<sup>a</sup> Not included in P value calculation to assess differences.

<sup>b</sup> Significant when nonsmokers are excluded in the analysis of variance (P < .001).

Table 2. Logistic Regression Models for COVID-19 Outcomes by Smoking Status Among the Cohort

Outcome	Odds ratio (95% CI)		
	Unadjusted	Adjusted for age, race, and gender	Adjusted for age, race, gender, medication, <sup>a</sup> and comorbidity <sup>b</sup>
<b>Hospitalization given a positive COVID-19 test</b>			
Never smoker	1 [Reference]	1 [Reference]	1 [Reference]
0-10 Pack-years	1.41 (1.10-1.81)	0.99 (0.76-1.30)	0.96 (0.70-1.30)
10-30 Pack-years	2.48 (2.01-3.07)	1.41 (1.12-1.78)	1.16 (0.85-1.58)
>30 Pack-years	4.65 (3.72-5.82)	2.25 (1.76-2.88)	2.19 (1.52-3.14)
<b>ICU admission given a positive COVID-19 test and hospitalization</b>			
Never smoker	1 [Reference]	1 [Reference]	1 [Reference]
0-10 Pack-years	1.33 (0.84-2.08)	1.19 (0.75-1.89)	1.08 (0.65-1.79)
10-30 Pack-years	1.74 (1.23-2.45)	1.55 (1.09-2.21)	1.34 (0.86-2.13)
>30 Pack-years	2.11 (1.54-2.89)	1.69 (1.23-2.35)	1.34 (0.86-2.10)
<b>Death given a positive COVID-19 test</b>			
Never smoker	1 [Reference]	1 [Reference]	1 [Reference]
0-10 Pack-years	2.38 (1.50-3.80)	1.66 (0.98-2.83)	1.07 (0.59-1.94)
10-30 Pack-years	3.40 (2.31-5.02)	1.47 (0.96-2.27)	0.88 (0.51-1.52)
>30 Pack-years	6.11 (4.33-8.61)	1.89 (1.29-2.76)	1.26 (0.75-2.10)
<b>Per pack-year</b>			
Hospitalization	1.030 (1.026-1.034)	1.015 (1.011-1.019)	1.013 (1.007-1.019)
ICU admission	1.012 (1.007-1.016)	1.008 (1.003-1.013)	1.005 (0.999-1.012)
Death	1.026 (1.020-1.031)	1.007 (1.002-1.013)	1.003 (0.995-1.010)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

<sup>a</sup> Angiotensin receptor blockers and oral or inhaled corticosteroids.

<sup>b</sup> Coronary artery disease, chronic obstructive pulmonary disease or emphysema, hypertension, and diabetes.

Adults who tested positive for COVID-19 between March 8, 2020, and August 25, 2020, and who had full smoking information recorded were included in the cohort. We classified patients based on their cumulative recorded smoking exposure. Those who reported that they were never smokers were compared with patients reporting 0 to 10 pack-years, 10 to 30 pack-years, and more than 30 pack-years. Demographic differences between these groups and previous literature on the risk factors of adverse COVID-19 outcomes informed the study modeling.<sup>1,3,5,6</sup> We used multivariable logistic regression models to determine the odds ratio for hospitalization given a positive test, admission to the intensive care unit given hospitalization, and death given a positive COVID-19 test for each pack-year cohort compared with never smokers. Regression models were run unadjusted, adjusted for identified confounders (age, race, and gender) and adjusted for mediators (adding coronary artery disease, hypertension, chronic obstructive pulmonary disease, diabetes, use of angiotensin receptor blockers, and use of oral or inhaled corticosteroids). We used likelihood ratio tests to determine whether a given covariate would remain in the model.

**Results** | Of the 7102 patients included in the cohort, 6020 (84.8%) were never smokers, 172 (2.4%) were current smokers, and 910 (12.8%) were former smokers. All demographics are summarized in **Table 1**, and the results of logistic regression analyses are summarized in **Table 2**. The findings showed a dose-response association between pack-years and adverse COVID-19 outcomes. Patients who smoked more than 30 pack-years had a 2.25 times higher odds of hospitalization (95% CI, 1.76-2.88), and these heavy smokers were 1.89 times more likely to die following a COVID-19 diagnosis (95% CI, 1.29-1.76) when

compared with never smokers. The association between cumulative smoking and adverse COVID-19 outcomes is likely mediated in part by comorbidities. The odds ratios for all adverse outcomes were attenuated in the mediation models. There was no evidence of effect modification by smoking status; similar odds ratios were seen in both current and former smokers.

**Discussion** | The results of this study suggest that cumulative exposure to cigarette smoke is an independent risk factor for hospital admission and death from COVID-19. Smoking is imperfectly classified in patient electronic medical records, and former smokers are potentially classified as never smokers, while pack-years may be underrecorded. However, this misclassification is likely to bias the present results toward the null, which would underestimate the association of cigarette smoking on adverse COVID-19 outcomes. The limitations on who has access to care at tertiary medical centers in the United States prevent generalizability to the whole population. The patients with complete data in this study are likely to be wealthier and have more consistent access to health care, as pack-years of smoking was typically collected during previous visits to the Cleveland Clinic. Nevertheless, we have demonstrated in this single central registry of patients who tested positive for COVID-19 that increased cumulative smoking was associated with a higher risk of hospitalization and mortality from COVID-19 in a dose-dependent manner.

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**Accepted for Publication:** November 7, 2020.

**Published Online:** January 25, 2021. doi:10.1001/jamainternmed.2020.8360

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**Author Contributions:** Ms Lowe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design:* All authors.

*Acquisition, analysis, or interpretation of data:* All authors.

*Drafting of the manuscript:* Lowe, Hatipoğlu, Attaway.

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All authors.

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*Administrative, technical, or material support:* Hatipoğlu

*Supervision:* Zein, Hatipoğlu, Attaway.

**Conflict of Interest Disclosures:** Dr Hatipoğlu reports receiving royalties from Wolters Kluwer Health for his work as section editor for UpToDate. No other disclosures were reported.

**Funding/Support:** Research support was provided through a grant from the National Institutes of Health's National Heart, Lung, and Blood Institute (K08HL133381).

**Role of the Funder/Sponsor:** The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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