The impact of smoking status and smoking-related comorbidities on COVID-19 patient outcomes: A causal mediation analysis

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Abstract:

Introduction:

Smoking history is a known risk factor for significant chronic diseases as well as pulmonary infections; however, the impact of smoking status on COVID-19 outcomes has not been conclusively characterized. This study aims to evaluate the association of smoking status on COVID-19 outcomes, and to explore the mechanism by which smoking and smoking-related comorbidities relate to COVID-19 outcomes.

Methods: Patients admitted with SARS-CoV-2 infection from November 2020 through January 2021 were included in this study. Causal mediation models investigating the associations between smoking status and the outcomes of mortality, intensive care unit (ICU) admission, advanced respiratory support, mechanical ventilation, ICU length of stay, and hospital length of stay, through mediation via smoking-related comorbidities, were examined.

Results: Active smokers did not experience worse COVID-19 outcomes once hospitalized. Former smokers had a higher odds of mortality (total effect OR 1.59, 95% CI 1.07-2.38, p=.01; indirect effect OR 1.45, 95% CI 1.09-1.93, p<.001), and advanced respiratory support (total effect OR 1.31, 95% CI 1.04-1.67, p=.02; indirect effect OR 1.26, 95% C1.03-1.54, p=.02), which were mediated by smoking-related comorbidities. While there was a non-significant increase in the total effect for mechanical ventilation, smoking-related comorbidities were significant mediators for their increased need (total effect OR 1.40, 95% CI 0.92-2.14, p=.13; indirect effect OR 1.47, 95% CI 1.10-1.87, p<.001).

Conclusion: While active smokers did not experience worse COVID-19 outcomes compared to never smokers, these results should be interpreted with caution. Compared to never smokers, former smokers had greater odds of mortality, advanced respiratory support, and

mechanical ventilation which was significantly mediated through smoking-related comorbidities.

Implications:

Previous studies have linked smoking status with worse COVID-19 outcomes, and have inferred that smoking-related comorbidities may play a role in these findings. This causal mediation analysis provides statistical evidence supporting this hypothesis, clarifying the risk that smoking-related comorbidities impart on COVID-19 outcomes in those with a smoking history.

Introduction:

Coronavirus disease 2019 (COVID-19) is a viral, pulmonary infection caused by the SARS-CoV-2 virus. COVID-19 has a variable presentation, ranging from asymptomatic infection to critical illness with subsequent complications of acute respiratory distress syndrome, cytokine storm syndrome, and multiorgan system failure.[1,2] Risk factors associated with severe illness have been identified to include advanced age, obesity, and underlying comorbidities.[3]

Though smoking is a well-established risk factor for viral pulmonary infections, its relationship with COVID-19 infection and severity has been unclear and at times contradictory. Early observational studies reported lower rates of COVID-19 infection among active smokers[4–7] or failed to detect associations between worse COVID-19 outcomes and active smoking.[8–11] In contrast, other studies have detected an increase in risk of disease severity with smoking.[12–14] Positive dose-dependent responses has been identified between pack-years and adverse COVID-19 outcomes, signaling the importance of quantifying smoking exposure intensity and duration.[15,16] Mendelian randomization studies exploring causal relationships between genetic variants predicting smoking initiation and intensity with COVID-19 infection risk and disease severity have shown that those genetically predisposed to smoking fair worse.[17,18] And from a mechanistic standpoint, angiotensin converting enzyme-2 (ACE2), the primary receptor by which SARS-CoV-2 enters the cell, has been shown to be upregulated in smokers,[19–21] with studies finding nicotine exposure playing a role in potentiating viral cellular uptake through this receptor.[22–24]

What has been a more consistent finding in current literature is the evidence that former smokers have worse disease outcomes compared to non-smokers and active smokers.[7,8,10–12,16,25] As former smokers often are older in age, with a tendency for longer exposure to tobacco in their lifetimes, they also have a higher burden of chronic disease. With regard to chronic comorbidities, prolonged and repeated exposure to smoking is associated with the development of respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea, and lung cancer.[26] Smoking is also associated with increased risk of numerous non-respiratory diseases, such as diabetes mellitus,[27] coronary artery disease,[27,28] cerebrovascular disease,[29] kidney disease,[30] and other malignancies.[27]

As smoking is inextricably linked to pulmonary health and significant comorbid conditions - both of which are important determinants of COVID-19 severity - disentangling these associations is important to better understand the mechanisms which lead to worse COVID-19 outcomes. While prior studies have proposed that worse outcomes, specifically in former smokers, are attributable to long term sequelae of smoking and consequent smoking-related disease, dedicated analysis exploring this relationship is missing from current literature.[8,12,25]

Mediation analysis provides an analytic tool by which causal explanation can be explored, to further clarify the mechanisms behind smoking history and worse COVID-19 outcomes. Therefore, the aim of this study is to describe the associations between smoking status and COVID-19 severity, and to estimate the causal impact of smoking-related comorbidities within these relationships.

Methods:

In this retrospective, observational, cohort study, patients admitted with and treated for COVID-19 disease at three hospitals within a North Philadelphia academic medical institution between November 1, 2020 and January 31, 2021 were included. All patients had laboratory confirmed COVID-19 infection by reverse-transcriptase polymerase chain reaction (RT-PCR) assay of nasal swab specimens. Demographic information, comorbidities, clinical signs and symptoms, and outcome data were obtained through chart review of the electronic medical record (EMR). Patients were excluded from this study if they were younger than 18, had a hospital stay less than 24 hours, or had missing smoking status information. Patients were categorized as either being active, former, or never smokers, as captured in the EMR through patient-report. Active smokers were defined as individuals currently smoking any quantity of tobacco products on a regular and ongoing basis. Former smokers were defined as individuals with any previous smoking history and no ongoing use at the time of admission. Never smokers were defined as individuals who denied any use of tobacco products in their lifetime. Advanced respiratory support was defined as an oxygen requirement in excess of simple nasal cannula (with a maximum flow rate of 6 liters per minute). This study received institutional review board approval (protocol 27050).

Causal mediation analysis was performed for relevant smoking-related comorbidities (diabetes mellitus [DM], chronic obstructive pulmonary disorder [COPD], asthma, chronic kidney disease [CKD], end-stage-renal disease [ESRD], obstructive sleep apnea [OSA], coronary artery disease [CAD], stroke, and history of malignancy). Smoking-related comorbidities were qualified based on biological plausibility and existing evidence in literature. Mediation models were constructed for the outcomes of mortality, intensive care

unit (ICU) admission, ICU length of stay, hospital length of stay, advanced respiratory support, and mechanical ventilation. The exposures examined, in separate models, were of former smokers vs. never smokers, and active smokers vs. never smokers. The mediators of interest were defined as dichotomous variables indicative of the presence of smoking-related comorbidities. In this mediation analysis, the overall effect of smoking on subsequent COVID-19 outcomes, was decomposed into a natural indirect effect, representing the smoking-related comorbidities mechanism, and the direct effect, representing all other potential mechanisms **(Figure 1)**. Additional analysis was performed on patients with any smoking history (former or active), and were grouped as "ever smokers." Sensitivity analysis was conducted for those in the former smoker group who had quit smoking greater than 90 days before presentation to account for patients self-reporting "former smoker" status despite recent smoking exposure.

Statistical Analysis

Continuous patient data were expressed with means (standard deviation [SD]) or medians (interquartile range). Categorical data were expressed as absolute and relative frequency. Normally distributed continuous variables were compared with the use of two-sample *t*-test or analysis of variance. Non-normally distributed continuous variables were compared with the use of Kruskal-Wallis test. Categorical variables were compared with the use of the Pearson chi-square test. Univariate analyses were performed with the use of SAS 9.4 (SAS Institute, Cary, NC).

Mediation analyses were performed using R version 4.1.2 and Inverse Odds Ratio Weighting.[31] We chose to use this approach because it is advantageous when there are multiple mediators, as in our analysis, as it proposes a model for smoking status and for each of the outcomes, but not for the mediators. Because of this, the mediators can be categorical, discrete, or continuous. In addition, the approach is ideal when the outcome model is a generalized linear model, as is the case for all of our outcomes. In using this approach, the total effect is decomposed into a natural indirect effect due to all the mediators together and a natural direct effect that is due to potential mechanisms other than the mediators. It should be noted that limitations of this approach are that we cannot obtain indirect effect estimates for each of the mediators individually. Also, this approach does not allow for an interaction effect between smoking status and the mediators. All models (for the exposure and each of the outcomes) controlled for age, sex, and race. The model for the exposure was specified as a multinomial logistic regression because there are three categories (active smoker, never smoker, former smoker) and the reference group was specified as never smokers. We then compared active smokers to never smokers and former smokers to never smokers. The models for the outcome were specified according to the distribution of each of the outcomes. Specifically, we specified a logistic model for mortality, ICU admission, advanced respiratory support, and mechanical ventilation, and a Poisson model for hospital length of stay. For ICU length of stay, we specified a normal regression model fit to the log of ICU length of stay because the ICU length of stay was measured as a continuous variable but could not go below zero and was therefore skewed. However, the log of ICU length of stay followed a normal distribution. The model for ICU length of stay was fit only to those admitted to the ICU. All 95% confidence intervals were constructed using bootstrapping; likewise, p-values are based on the bootstrap. All statistical tests were two-tailed, and $\alpha = .05$ was used to indicate statistical significance.

Results:

A total of 1556 patients were included in the study. Of this cohort, the mean (±SD) age was 60.4±16.48 years, 784 (50.4%) were female, and 575 (37.0%) were Black, non-Hispanic. With regard to smoking history, 869 (55.8%) were never smokers, 499 (32.1%) were former smokers, and 188 (12.1%) were active smokers.

The mean age of active smokers (55.1±13.49 years) was younger than former smokers (66.4±13.58 years) and never smokers (58.1±17.60 years). Active smokers had the highest percentage of males (63.3%) compared to former (52.9%) and never smokers (44.8%). Active smokers also had the highest percentage of Black, non-Hispanic patients (53.7%) compared to former (41.3%) and never smokers (30.8%). Former smokers had a higher number of smoking-related comorbidities (2.7±1.66) compared to active (1.9±1.63) and never smokers (1.8±1.47).

Active smokers presented less frequently with shortness of breath (active: 54.8%, former: 65.5%, never: 60.3%), cough (active: 50.5%, former: 62.3%, never: 64.0%), fever (active: 33.5%, former: 45.9%, never: 46.0%), loss of taste and smell (active: 9.0%, former: 14.0%, never: 16.6%), and fatigue (active: 29.3%, former: 45.7%, never: 41.8%) compared to former and never smokers. There were no differences in gastrointestinal symptoms, including nausea/vomiting and diarrhea, among all three groups. Never smokers were less likely to require advanced respiratory support (8.7%) on initial admission to the hospital compared to

former (14.0%) and active smokers (9.6%). Baseline demographic and symptom data are detailed in **Table 1.**

Throughout hospitalization, former smokers had a greater need for advanced respiratory support (former: 25.9%, active: 21.8%, never: 17.5%), as well as mechanical ventilation (former: 10.0%, active: 7.4%, never: 5.9%), compared to active and never smokers. Former smokers also had the highest rate of ICU admission (former: 20.6%, active: 14.9%, never: 13.3%) and mortality (former: 11.6%, active: 5.9%, never: 5.5%). For patients requiring ICU admission, there were no differences in ICU length of stay among the smoking groups. Former smokers had the longest mean in-hospital length of stay (8.0±9.13 days) compared to never smokers (6.4±6.83 days) and active smokers (6.1±5.45 days). Detailed outcome results are presented in **Table 2**.

Mediation analysis was performed to determine whether the effect of smoking status, particularly of former smoking status, was mediated by smoking-related comorbidities. With regard to the total effect, former smokers were found to have 1.59 times greater odds of mortality, with adjustment for age, sex, and race/ethnicity, compared to never smokers (95% CI 1.07-2.38, p=.01). The indirect effect, or the effect of mortality attributed to smoking-related comorbidities along the proposed causal pathway was significant (indirect effect OR 1.45, 95% CI 1.09-1.93, p<.001), with 82.7% of the total effect mediated by smoking-related comorbidities for former smokers. The direct effect of former smoking status on mortality, or the effect that does not go through the proposed causal pathway, was non-significant (direct effect OR 1.10, 95% CI 0.68-1.77, p=.65). For the outcome of requiring advanced respiratory support during hospitalization, former smokers had 1.31 times greater odds, compared to

never smokers for the total effect in the adjusted model (95% CI 1.04-1.67, p=.02). The indirect effect, or the effect of mortality attributed to smoking-related comorbidities, was also significant (indirect effect OR 1.26, 95% CI 1.03-1.54, p=.02).

While no significant total effect was identified for former smokers and the outcome of mechanical ventilation, the indirect effect was significant. Former smokers had a total effect OR of 1.40 (95% CI 0.92-2.14, p=.13) compared to never smokers, while the indirect effect via smoking-related comorbidities for mechanical ventilation was statistically significant (indirect effect OR 1.47, 95% CI 1.10-1.87, p<.001).

Formers smokers also had greater odds for ICU admission (total effect OR 1.35, 95% CI 1.04-1.81, p=.01; indirect effect OR 1.16, 95% CI 0.95-1.46, p=.18) and increased hospital length of stay (total effect OR 1.14, 95% CI 1.02-1.33, p=.03; indirect effect OR 1.06, 95% CI 0.97-1.15, p=.16) for the total effects only, compared to never smokers.

No significant effects for active smokers (vs. never smokers) were identified for the outcomes of mortality, ICU admission, advanced respiratory support, mechanical ventilation, or hospital length of stay. Active smokers did, however, have a statistically significant decrease in ICU length of stay, compared to never smokers through mechanisms unrelated to smoking-related comorbidities (total effect OR 0.66, 95% CI 0.38-0.96, p=.03; direct effect OR 0.25, 95% CI 0.09-0.80, p<.001).

Ever smokers, or the combined active and former smoker group, were found to have greater odds for mortality for both the total effect and the indirect effect of smoking-related comorbidities (total effect OR 1.53, 95% CI 1.07-2.27, p=.03; indirect effect OR 1.27, 95% CI 1.02-1.60, p=.04). Ever smokers also had greater risk for ICU admission for the total effect only (total effect OR 1.30, 95% CI 1.02-1.72, p=.02; indirect effect OR 1.14, 95% CI 0.98-1.38, p=.11). Ever smokers had greater odds for advanced respiratory support (total effect OR 1.32, 95% CI 1.00-1.68, p=.05; indirect effect OR 1.19, 95% CI 1.04-1.40, p=.01) and mechanical ventilation (total effect OR 1.34, 95% CI 0.95-1.99, p=.10; indirect effect OR 1.28, 95% CI 1.04-1.63, p=.01); however, the total effect did not reach significance even though the indirect effects through smoking-related comorbidities were significant. No significant associations were identified for ever smokers and hospital length of stay or ICU length of stay. Causal mediation analysis results are detailed in **Table 3**.

Sensitivity analysis was performed for the former smoker group, examining only former smokers for whom quit duration was both available and greater than 90 days. Of the 499 former smokers, 34 (7%) were missing data on quit duration, and 10 (2%) had quit smoking within 90 days of hospital admission. After restricting analysis to these 455 former smokers, there remained a statistically significant association for increase in risk of mortality (total effect OR 1.52, 95% CI 0.99-2.33, p=.06; indirect effect OR 1.47, 95% CI 1.15-1.97, p<.001), advanced respiratory support (total effect OR 1.32, 95% CI 0.99-1.78, p=.06; indirect effect OR 1.33, 95% CI 1.03-1.69, p=.01), and mechanical ventilation (total effect OR 1.40, 95% CI 0.95-2.14, p=.12; indirect effect OR 1.49, 95% CI 1.16-2.05, p=.01) through the indirect effects only, and no longer in the total effects as was seen in the unrestricted former smoking group. Additionally, former smokers with quit duration greater than 90 days were not associated with increased risk of ICU admission, or ICU length of stay,

but did have an increased risk of hospital length of stay (total effect OR 1.14, 95% CI 0.97-1.30, p=.09; indirect effect OR 1.09, 95% CI 1.00-1.19, p=.04) through indirect effects only. Sensitivity analysis is detailed in **Supplementary Table 1.**

Discussion:

This study demonstrates the complexities of the relationship between smoking and COVID-19 disease. In our study, active smoking status was not associated with statistically significant negative outcomes which remains paradoxical given the viral and respiratory origins of COVID-19. However, these results are supported by findings of other studies[8,10] and meta-analyses[11] that specifically examine active smokers separate from former smokers. Additionally, we found that active smokers reported fewer respiratory symptoms, as well as a lower symptom burden compared to never and former smokers; however, this is in the context of a younger group with fewer comorbidities. The prevalence of active smokers in this cohort was also low at 12.1%, with respect to the city-wide smoking prevalence of 22.4%.[32] This is congruent with national and international reports of active smokers hospitalized with COVID-19 presenting at a lower rate compared to their respective populations,[4,33,34].

Possible mechanisms for these findings include a complex interplay of biochemical and biological processes which may yield net protective effects in some active smokers. For example, recent exposure to tobacco-related irritants can enhance innate protective mechanisms potentially effective against SARS-CoV-2, such as increasing ciliary beat frequency within the nasal tract[35] and increasing mucociliary clearance.[36] Chronic smoking

exposure, however, eventually results in ciliated epithelial cell loss, goblet cell hyperplasia, and mucous hypersecretion, ultimately impairing mucociliary clearance and limiting this protective defense mechanism.[37] The role of nicotine in modulating risk in active smokers has also been an important point of discussion. Nicotine has been shown to exert anti-inflammatory and positive immunomodulatory effects, specifically through the binding to acetylcholine receptor type 7 (α7nACHR).[38] Binding of this nicotinic receptor has a downstream effect of inhibiting the activation of the inflammatory NF-κB pathway and the production of pro-inflammatory cytokines.[39] As the dysregulated inflammatory response is largely responsible for severe illness in COVID-19, modulating this pathway may be beneficial. However, in direct contrast, recent in-vitro studies have found that ACE2 expression in pneumocytes is upregulated in the presence of nicotine, with resulting increases in SARS-CoV-2 infectivity.[22] Clinical trials investigating the therapeutic benefit of nicotine transdermal patches in hospitalized patients with COVID-19 are currently underway in France.[40] Furthermore, nitric oxide, which is produced during smoking, has been shown to inhibit SARS-CoV replication and penetration into cells, also potentially conferring protective effects.[41,42]

In this cohort, we found that former smokers were at greater risk for mortality, ICU admission, advanced respiratory support, as well as longer hospital length of stays compared to never and active smokers, corroborating the findings of other studies.[4,15,43] The underlying cause for this association has been hypothesized to be related to the increased age and comorbidities of former smokers compared to never and active smokers, with previous studies noting a reduction or elimination of negative associations following adjustment for age and comorbidities.[4,15,44] These studies signaled the important mediatory role comorbidities play, however did not go beyond simply acknowledging this observation. This

study directly tested this hypothesis through causal mediation analysis, finding that smoking-related comorbidities were significant mediators linking former smoker status with the outcomes of mortality, advanced respiratory support, and mechanical ventilation.

In the case of the "ever smoker" group, or the combined active and former smoker group, significant associations between any history of smoking and worse outcomes remained significant through the causal pathway of smoking-related comorbidities. These results support the hypothesis that smoking is associated with worse outcomes, predominately in cases where smoking has resulted in smoking-related disease.

One concern of using self-reported smoking status is the validity of the classification, especially with regard to former smoking status. For example, active smokers may incorrectly identify themselves as former smokers after recently discontinuation of smoking with the onset of symptoms, or after presenting to the hospital and subsequently deciding to quit. In our study, we found that only 10 patients had reported a quit date within the last 90 days, with 34 patients missing this information, only representing 8% of the former smoker cohort. In sensitivity analysis, when the former smoker group was restricted to those who had quit smoking greater than 30 days from the time of admission and with exclusion of those missing quit duration data, the indirect effects through smoking-related comorbidities persisted for the outcomes of mortality, advanced respiratory support, mechanical ventilation, and found additional significant associations with an increase in hospital length of stay.

In and of itself, former smoking status does not explain the increased risk of mortality, but rather, the sequelae of historical smoking in the form of chronic comorbidities, are prevalent

causal factors. With active smokers, this effect is not observed, and is supported by the fact that active smokers presented with far fewer comorbidities compared to former smokers. This is possibly explained by active smokers being younger in age than former smokers, as well as active smokers likely not having yet developed smoking-related complications, which is a leading motivator for smoking cessation.[45]

It is also important to emphasize that active and former smokers are distinctive groups, especially when evaluating COVID-19 risks. Many prior studies have combined active smokers and former smokers into one category for smoking exposure, however, this broad over simplification of smoking exposure may misrepresent the risks associated with *any* smoking history.[43,46] This is particularly the case when it comes to understanding the main drivers of the associations between smoking history and COVID-19 outcomes, as former smokers and active smokers often represent groups with very different characteristics. Ultimately, high quality data is needed to capture smoking duration, intensity, and frequency to better quantify risks associated with smoking and smoking exposure; however, collection of this data remains challenging particularly for patients presenting in respiratory distress or critical condition.

There are several limitations to this study. First, smoking status information was obtained retrospectively from the electronic medical record and was patient reported. As such, reported never smoker and former smoker status designation may be interpretable in different ways by patients and these discrepancies may lead to misclassification of their smoking history. This analysis was based on categorical smoking status designation, as opposed to more descriptive smoking history, such as pack-year history, duration of smoking period, intensity of smoking

habits, or smoking modality, due to data unavailability in the EMR. This study was performed in a single institution in an urban environment in the United States, and is therefore not generalizable to other populations. Only patients with a hospital admission greater than 24 hours were included in this study, excluding patients who were unable to present to the hospital for care, or who did not meet criteria for admission due to milder symptom severity.

Conclusion:

Overall, this study provides evidence on the associations between smoking status and COVID-19 outcomes. While active smokers were unexpectedly not associated with statistically significantly worse COVID-19 outcomes, former smokers were associated with an increased risk of mortality, advanced respiratory support, and mechanical ventilation through the mediators of smoking-related comorbidities. Results from this causal mediation analysis supports the role of smoking-related comorbidities as an integral factor for worse outcomes in former smokers. Therefore, smoking and subsequent development of smoking-related comorbidities increases the risk for worse outcomes in COVID-19. Smoking cessation, and better yet smoking abstinence, should continue to be advocated for, particularly in the context of the COVID-19 pandemic.

Data Availability:

The data that support the findings of this study are available from the corresponding author, CL, upon reasonable request.

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Declaration of Interests:

The authors declare that they do not have any potential conflicts of interest regarding this submitted manuscript.

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Table 1: Patient baseline demographics, comorbidities, and presenting symptoms

	Smoking History				
	Never smoker (N=869)	Active smoker (N=188)	Former smoker (N=499)	Total (N=1556)	P-value
Age					<.0001[1]
Mean (SD)	58.1 (17.60)	55.1 (13.49)	66.4 (13.58)	60.4 (16.48)	
Median (IQR)	59.0 (47.0, 71.0)	57.0 (46.0, 65.0)	67.0 (58.0, 76.0)	62.0 (50.0, 72.0)	
Sex, n (%)					<.0001[2]
Female	480 (55.2%)	69 (36.7%)	235 (47.1%)	784 (50.4%)	
Male	389 (44.8%)	119 (63.3%)	264 (52.9%)	772 (49.6%)	
Race/Ethnicity, n (%)					<.0001[2]
Black, non-Hispanic	268 (30.8%)	101 (53.7%)	206 (41.3%)	575 (37.0%)	
Asian, non-Hispanic	59 (6.8%)	3 (1.6%)	10 (2.0%)	72 (4.6%)	
White, non-Hispanic	128 (14.7%)	27 (14.4%)	101 (20.2%)	256 (16.5%)	
Hispanic	314 (36.1%)	44 (23.4%)	132 (26.5%)	490 (31.5%)	
Other race	54 (6.2%)	5 (2.7%)	24 (4.8%)	83 (5.3%)	
Unknown	46 (5.3%)	8 (4.3%)	26 (5.2%)	80 (5.1%)	
Comorbidities, n (%)					
Hypertension	558 (64.2%)	115 (61.2%)	387 (77.6%)	1060 (68.1%)	<.0001[2]
Congestive heart failure	88 (10.1%)	23 (12.2%)	84 (16.8%)	195 (12.5%)	0.0015[2]
History of stroke	56 (6.4%)	21 (11.2%)	80 (16.0%)	157 (10.1%)	<.0001[2]
Diabetes mellitus	342 (39.4%)	67 (35.6%)	247 (49.5%)	656 (42.2%)	0.0002[2]
Chronic kidney disease	115 (13.2%)	28 (14.9%)	117 (23.4%)	260 (16.7%)	<.0001[2]
End-stage renal disease	25 (2.9%)	7 (3.7%)	27 (5.4%)	59 (3.8%)	0.0614[2]
COPD	33 (3.8%)	38 (20.2%)	117 (23.4%)	188 (12.1%)	<.0001[2]
Asthma	153 (17.6%)	38 (20.2%)	93 (18.6%)	284 (18.3%)	0.6781[2]
Obstructive sleep apnea	92 (10.6%)	14 (7.4%)	97 (19.4%)	203 (13.0%)	<.0001[2]
Malignancy	97 (11.2%)	9 (4.8%)	105 (21.0%)	211 (13.6%)	<.0001[2]
Number of comorbidities					<.0001[1]
Mean (SD)	1.8 (1.47)	1.9 (1.63)	2.7 (1.66)	2.1 (1.61)	
Median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (2.0, 4.0)	2.0 (1.0, 3.0)	

	Smoking History				
	Never smoker (N=869)	Active smoker (N=188)	Former smoker (N=499)	Total (N=1556)	P-value
Symptoms, n (%)					
Cough	556 (64.0%)	95 (50.5%)	311 (62.3%)	962 (61.8%)	0.0026[2]
Shortness of breath	524 (60.3%)	103 (54.8%)	327 (65.5%)	954 (61.3%)	0.0236[2]
Loss of taste/smell	144 (16.6%)	17 (9.0%)	70 (14.0%)	231 (14.8%)	0.0258[2]
Fatigue	363 (41.8%)	55 (29.3%)	228 (45.7%)	646 (41.5%)	0.0005[2]
Fever	400 (46.0%)	63 (33.5%)	229 (45.9%)	692 (44.5%)	0.0055[2]
Syncope	47 (5.4%)	3 (1.6%)	19 (3.8%)	69 (4.4%)	0.0502[2]
Diarrhea	224 (25.8%)	43 (22.9%)	119 (23.8%)	386 (24.8%)	0.5882[2]
Nausea/vomiting	216 (24.9%)	39 (20.7%)	105 (21.0%)	360 (23.1%)	0.1939[2]
Initial oxygen requirement, n (%)					<.0001[2]
Room air	582 (67.0%)	122 (64.9%)	260 (52.1%)	964 (62.0%)	
Nasal cannula	211 (24.3%)	48 (25.5%)	169 (33.9%)	428 (27.5%)	
High flow nasal cannula	55 (6.3%)	8 (4.3%)	51 (10.2%)	114 (7.3%)	
BiPAP	16 (1.8%)	6 (3.2%)	15 (3.0%)	37 (2.4%)	
Mechanical ventilation	5 (0.6%)	4 (2.1%)	4 (0.8%)	13 (0.8%)	
Initial advanced respiratory support, n (%)	76 (8.7%)	18 (9.6%)	70 (14.0%)	164 (10.5%)	0.0083[1]

[1]Kruskal-Wallis p-value; [2]Chi-Square p-value;

Abbreviations – SD: standard deviation, IQR: interquartile range, COPD: chronic obstructive pulmonary disease, BiPAP: Bilevel positive airway pressure

Table 2: Patient outcomes of interest

	Smoking History				
	Never smoker (N=869)	Active smoker (N=188)	Former smoker (N=499)	Total (N=1556)	P-value
ICU Admission, n (%)	116 (13.3%)	28 (14.9%)	103 (20.6%)	247 (15.9%)	0.0017[1]
Mortality, n (%)	48 (5.5%)	11 (5.9%)	58 (11.6%)	117 (7.5%)	0.0001[1]
Advanced respiratory support, n (%)	152 (17.5%)	41 (21.8%)	129 (25.9%)	322 (20.7%)	0.0011[1]
Mechanical ventilation, n (%)	51 (5.9%)	14 (7.4%)	50 (10.0%)	115 (7.4%)	0.0185[1]
Hospital length of stay, days					<.0001[2]
Mean (SD)	6.4 (6.83)	6.1 (5.45)	8.0 (9.13)	6.9 (7.55)	
Median (IQR)	4.0 (3.0, 7.0)	4.0 (3.0, 7.0)	5.0 (3.0, 9.0)	5.0 (3.0, 8.0)	
	Never smoker (N=116)	Active smoker (N=28)	Former smoker (N=103)	Total (N=247)	
ICU length of stay, days					0.0647[2]
Mean (SD)	10.7 (10.83)	6.5 (7.57)	10.4 (11.72)	10.1 (10.94)	
Median (IQR)	7.2 (2.9, 16.4)	4.2 (1.2, 7.8)	6.8 (2.8, 15.9)	6.6 (2.8, 14.9)	

[1]Chi-Square p-value; [2]Kruskal-Wallis p-value;

Abbreviations – SD: standard deviation, IQR: interquartile range, ICU: Intensive care unit

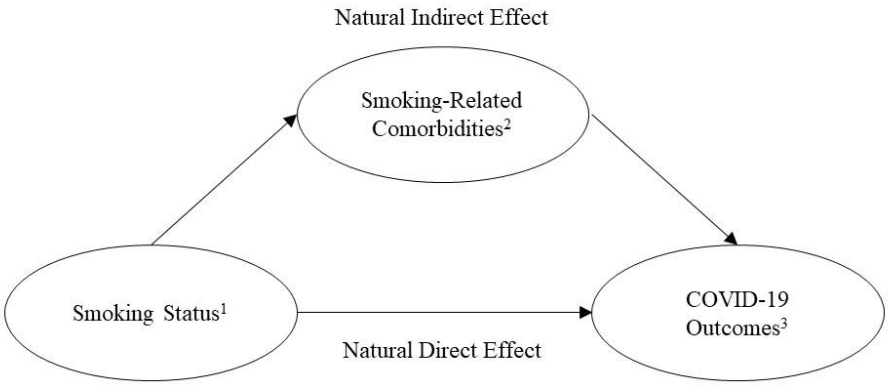
Table 3: Causal mediation analysis of outcomes of interest by smoking history, with adjustment for age, sex, and race.

	Active Smoker[†]			Former Smoker[†]		
	OR	(95% CI)	p Value	OR	(95% CI)	p Va
ICU admission						
Total effect	1.15	(0.68-1.80)	0.55	1.35	(1.04-1.81)	
Natural direct effect	1.23	(0.52-2.09)	0.73	1.17	(0.83-1.66)	
Natural indirect effect	0.93	(0.59-1.93)	1.00	1.16	(0.95-1.46)	
Mortality						
Total effect	1.25	(0.61-2.26)	0.53	1.59	(1.07-2.38)	
Natural direct effect	1.48	(0.29-2.88)	0.56	1.10	(0.68-1.77)	
Natural indirect effect	0.84	(0.44-2.68)	0.84	1.45	(1.09-1.93)	
Advanced respiratory support						
Total effect	1.36	(0.90-2.03)	0.15	1.31	(1.04-1.67)	
Natural direct effect	1.29	(0.65-2.11)	0.45	1.04	(0.75-1.48)	
Natural indirect effect	1.05	(0.73-1.70)	0.77	1.26	(1.03-1.54)	
Mechanical ventilation						
Total effect	1.18	(0.54-2.02)	0.76	1.40	(0.92-2.14)	
Natural direct effect	1.29	(0.35-2.59)	0.65	0.95	(0.60-1.58)	
Natural indirect effect	0.91	(0.43-2.25)	0.87	1.47	(1.10-1.87)	
Hospital length of stay						
Total effect	0.95	(0.84-1.11)	0.50	1.14	(1.02-1.33)	
Natural direct effect	0.92	(0.77-1.10)	0.27	1.08	(0.95-1.26)	
Natural indirect effect	1.03	(0.92-1.19)	0.63	1.06	(0.97-1.15)	
ICU length of stay						
Total effect	0.66	(0.38-0.96)	0.03	0.10	(0.78-1.30)	
Natural direct effect	0.25	(0.09-0.80)	<0.001	0.90	(0.61-1.37)	
Natural indirect effect	2.68	(0.84-8.13)	0.14	1.10	(0.80-1.49)	

The total effect of the association between smoking status and outcomes of interest are decomposed into the natural indirect effect, due to the mediators of smoking-related co

[†] Compared to never smokers

Abbreviations – ICU: Intensive care unit



[1]Separate models were examined comparing current smokers to never smokers, former smoker to never smokers, and ever smokers to never smokers.
[2]Smoking-related co-morbidities included diabetes mellitus, chronic obstructive pulmonary disease, asthma, obstructive sleep apnea, chronic kidney disease, end-stage renal disease, coronary artery disease, stroke, and malignancy.
[3]COVID outcomes examined in separate models include mortality, intensive care unit (ICU) admission, ICU length of stay, hospital length of stay, advanced respiratory support, and mechanical ventilation

Figure 1: Causal mediation model of COVID-19 outcomes and smoking-related comorbidities