



Association of smoking status with outcomes in hospitalised patients with COVID-19

Muhammad Adrish ¹, Sridhar Chilimuri,¹ Nikhitha Mantri,¹ Haozhe Sun,¹ Maleeha Zahid,¹ Sudharsan Gongati,¹ Ked Fortuzi,¹ Abhishrut Pramod Jog,¹ Pravish Purmessur,¹ Ravish Singhal²

To cite: Adrish M, Chilimuri S, Mantri N, *et al.* Association of smoking status with outcomes in hospitalised patients with COVID-19. *BMJ Open Res* 2020;7:e000716. doi:10.1136/bmjresp-2020-000716

Received 15 July 2020

Revised 10 September 2020

Accepted 15 September 2020

ABSTRACT

Introduction Smoking causes inflammation of the lung epithelium by releasing cytokines and impairing mucociliary clearance. Some studies have linked smoking with severity of illness of COVID-19 whereas others have found no such association.

Methods This was a retrospective analysis of all adults hospitalised with COVID-19 from 9 March to 18 May 2020.

Results 1173 patients met the study criteria. 837 patients never smoked whereas 336 patients were either current smokers or past smoker and were grouped together in smokers group. Patients in smokers group were more likely to be male and had higher incidence of underlying chronic obstructive pulmonary disease (19% vs 6%, $p<0.001$), HIV infection (11% vs 5%, $p<0.001$), cancer (11% vs 6%, $p=0.005$), congestive heart failure (15% vs 8%, $p<0.001$), coronary artery disease (15% vs 9%, $p=0.3$), chronic kidney disease (11% vs 8%, $p=0.037$) and end-stage renal disease (10% vs 6%, $p=0.009$) compared with non-smokers. Outcome analysis showed that smokers were more likely to develop critical illness requiring mechanical ventilation (47% vs 37% $p=0.005$). Univariate Cox model for survival analysis by smoking status showed that among smokers only current smokers had higher risk of death compared with never smokers (HR 1.61, 95% CI 1.22 to 2.12, $p<0.001$). In the multivariate approach, Cox model for the survival, female sex, young age, low serum lactate dehydrogenase and systemic steroid use were associated with overall improved survival.

Conclusion In our large single-centre retrospective database of patients hospitalised with COVID-19, smoking was associated with development of critical illness and higher likelihood of death.

INTRODUCTION

The coronavirus pandemic began in December 2019 and has rapidly spread globally.¹ The disease is caused by SARS-CoV-2, which belongs to the subgenus Sarbecovirus (Beta-CoV lineage B), Orthocoronavirinae subfamily.² SARS-CoV-2 predominantly affects the respiratory tract by entering the alveolar epithelial cells via ACE2 receptors. The virus also uses activation of spike proteins to enter the cells.³ Symptoms vary significantly from

Key Messages

- ▶ Does the smoking status affect outcomes of hospitalised patients with COVID-19.
- ▶ Our study shows that smokers are more likely to present with severe COVID-19 illness.
- ▶ Incidentally, we noted that system steroids use was independently associated with improved survival. We performed a subgroup analysis by disease severity to study this association further.

an asymptomatic infection to severe acute respiratory distress syndrome (ARDS).

Smoking has been considered a risk factor for many respiratory viral illnesses including influenza, MERS, RSV, and so on.^{4,5} Smoking leads to inflammation of the lung epithelium causing release of cytokines, increased mucous secretion, impaired mucociliary clearance as well as epithelial cell damage. In a descriptive study, Guan *et al*¹ showed that current and former smokers were more likely to present with severe COVID-19 compared with non-smokers. In another small study, Liu *et al*⁶ showed that smoking history was associated with progression of COVID-19. Contrary to these findings, study by Huang *et al*⁶ showed that current smoking history is not associated with need for intensive care unit care. Similar findings were observed by subsequent larger observational studies.^{7,8}

Nicotine is known to have a role in immunomodulation and regulation of ACE 2 receptors. In a recent study, ever smokers were shown to have higher pulmonary ACE2 receptor expression by 25% compared with never smokers. These findings suggested that ever smokers have increased risk of viral binding and entry into the lungs.⁹ Current literature evaluating difference in outcomes between current smokers, past smokers and never smokers is sparse. Our hospital is located in New York City where 13.1% of the



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¹Department of Medicine, Bronx Care Health System, Bronx, New York, USA

²Attending Pulmonary & Critical Care, Department of Medicine, Bronx Care Health System, Bronx, New York, USA

Correspondence to

Dr Muhammad Adrish; adrish@hotmail.com



residents' smoke.¹⁰ Bronx was also one of the hardest hit boroughs of the New York City during the COVID-19 pandemic.¹¹ In this retrospective study, we aimed to analyse the effects of smoking habits in the outcomes of patients hospitalised with COVID-19 illness. In view of recent literature suggesting improved mortality among hospitalised patients with COVID-19 who were treated with systemic steroids, we also aimed to assess the effects of the use of systemic steroids in our patient population.¹²

METHODS

Study setting

We conducted this study at BronxCare Health System, the largest voluntary, not-for-profit health and teaching hospital system, serving the south and central Bronx in the New York City. We retrospectively analysed all consecutively hospitalised adults with COVID-19 from 9 March to 18 May 2020. A diagnosis of COVID-19 was established when a patient tested positive for the virus SARS-CoV-2 from the PCR analysis of nasopharyngeal swab specimens at any point during their hospitalisation. Need for consent was waived due to retrospective nature of the study.

Participants and eligibility criteria

We included adult patients (aged 18 and above) with known smoking status who were hospitalised with COVID-19 for whom severity of illness could be established and had final disposition status at the time of the study. One thousand three hundred and thirty-six adult patients were admitted with COVID-19 during the study period. Smoking status was not known for 112 patients. Another 34 patients were still admitted at the time of data analysis and were excluded. Seventeen patients were excluded because the disease severity could not be established due to missing data elements. One thousand one hundred and seventy-three (87.8%) patients met the study inclusion criteria.

During the study period, an inpatient guide for the management of COVID-19 was developed by the Department of Medicine, and distributed to all healthcare providers at our hospital. Patients admitted during the study period received supportive and therapeutic modalities based on individual physician's clinical discretion and our inpatient guide. Based on early findings by Wu *et al*,¹³ use of systemic steroids (intravenous methylprednisolone) was suggested for patients with COVID-19 induced ARDS. Steroid use was also permitted for non-COVID-19 related illnesses such as exacerbation of obstructive airway diseases. Use of tocilizumab was suggested in patients with evidence of disease progression (defined as worsening respiratory status or radiographic findings) and increasing inflammatory markers early in their acute COVID-19 illness.¹⁴

We extracted our data manually from electronic medical records. The data obtained included patients' demographic details, comorbidities, self-reported

smoking history, laboratory and radiological test results (at admission or first available), medication administration history, and ventilator requirement data.

Study outcomes were defined as severity of illness and mortality.

Severity of respiratory illness

Severity of illness data was obtained at the worst clinical state during patient admission and was defined as follows:

- ▶ Hypoxia was defined as new-onset oxygen saturation of $\leq 94\%$.
- ▶ Mild illness was defined as upper respiratory illness without any evidence of pneumonia or hypoxia.
- ▶ Moderate illness was defined as radiographic evidence of pneumonia without hypoxia.
- ▶ Severe illness was defined as radiographic evidence of pneumonia with hypoxia requiring any form of supplemental oxygen or non-invasive positive pressure ventilation.
- ▶ Critical illness was defined as need for invasive mechanical ventilation.

Statistical analysis

We used univariate analysis χ^2 test for comparing categorical variables between smokers and non-smokers. Because the normality assumption was violated for continuous variables, the non-parametric Mood's median test was used to compare the two groups. To compare the survival times, log-rank test was used. Additionally, the Kaplan-Meier estimates were plotted.

In the multivariate approach, Cox model was used for modelling survival times with all baseline characteristics. In the Cox multivariate regression, stepwise backward selection was used with $p > 0.1$ for removal. The proportionality of the hazards assumption in a Cox model was tested using Schoenfeld residuals. We also performed a log rank analysis in critically ill patients to assess significance of systemic steroids. Statistical analyses were performed with the use of STATA software V.14.2.

RESULTS

One thousand one hundred and seventy-three patients met the study criteria and were included in final analysis. Of these, 837 (71.4%) patients never smoked and 336 (28.6%) were either current smokers or had smoked in the past. There was no difference between the smokers and non-smokers with regards to age or body mass index. Smokers were more likely to be males and African Americans. Smokers were more likely to have chronic obstructive pulmonary disease (19% vs 6%, $p < 0.001$), HIV infection (11% vs 5%, $p < 0.001$), cancer (11% vs 6%, $p = 0.005$), congestive heart failure (15% vs 8%, $p < 0.001$), coronary artery disease (15% vs 9%, $p = 0.027$), chronic kidney disease (11% vs 8%, $p = 0.04$), and end-stage renal disease (10% vs 6%, $p = 0.009$) compared with non-smokers (table 1). Smokers had higher median serum creatinine

Table 1 Baseline demographics of smokers and never smokers

	Smokers n=336	Never smokers n=837	P value
Age, years—median (IQR)	64 (54–73)	62 (52–73)	0.30
Sex—no (%)			
Female	87 (26%)	366 (44%)	<0.001
Male	249 (74%)	471 (56%)	
Ethnicity—no (%)			
Hispanic	183 (54%)	548 (66%)	<0.001
Black	114 (34%)	206 (25%)	
Caucasian	10 (3%)	6 (1%)	
Others	29 (9%)	77 (9%)	
BMI—median (IQR)*	28.6 (24.4–33.1)	28.9 (25.8–33.7)	0.69
Comorbidities—no (%)			
Hypertension	213 (63.4%)	524 (63%)	0.82
Diabetes mellitus	158 (47%)	377 (45%)	0.68
HIV infection/AIDS	37 (11%)	39 (5%)	<0.001
Asthma	52 (16%)	111 (13%)	0.62
COPD	64 (19%)	49 (6%)	<0.001
Chronic liver disease	5 (1.5%)	6 (1%)	0.38
Any cancer	36 (11%)	50 (6%)	0.005
Congestive heart failure	50 (15%)	66 (8%)	<0.001
Coronary artery disease	49 (15%)	78 (9%)	0.03
Chronic kidney disease	38 (11%)	63 (8%)	0.04
End-stage renal disease	35 (10%)	64 (6%)	0.009
Initial laboratory tests—median (IQR)*			
Absolute neutrophil count (ANC) (k/μL)	5.7 (3.7–8)	6.0 (4.1–8.3)	0.26
Absolute lymphocyte count (ALC) (k/μL)	0.8 (0.5–1.3)	0.9 (0.6–1.2)	0.69
ANC/ALC ratio	6.6 (4.0–11.6)	6.8 (4.3–11.4)	0.49
D-dimer (ng/mL)	536 (317–1025)	533 (304–1254)	0.95
Lactate dehydrogenase (μ/L)	490 (308–741)	483(350–690)	0.63
C-reactive protein (mg/L)	104.3 (46.6–181.4)	117.65 (62.42–198.70)	0.23
Ferritin (ng/mL)	752.6 (328.8–1466.5)	700.1 (364.6–1380.5)	0.40
Lactate (mmoles/L)	1.8 (1.3–2.55)	1.8 (1.3–2.5)	0.40
Creatinine (mg/dL)	1.2 (0.9–2.07)	1.0 (0.8–1.6)	<0.001
Alanine aminotransferase (unit/L)	29 (18–49)	29 (18–48)	0.99
Aspartate aminotransferase (unit/L)	49 (30–78)	46 (31–71.5)	0.056
Total protein (g/dL)	6.9 (6.5–7.6)	7.0 (6.5–7.5)	0.67
Serum albumin (g/dL)	3.6 (3.2–4)	3.6 (3.3–3.9)	0.68
Haemoglobin (g/dL)	13.2 (11.7–14.6)	13.2 (11.8–14.5)	0.89
White blood cell (k/μL)	7.3 (5.3–9.8)	7.5 (5.5–10.2)	0.32
Mean corpuscular volume (fL)	89.15 (84.9–93.1)	88 (83.7–91.7)	0.008
Mean corpuscular haemoglobin (pg)	33.4 (32.6–34.0)	33.3 (32.5–34.0)	0.24
Serum sodium (mEq/L)	136 (133–139)	137 (133–139)	0.38
Serum potassium (mEq/L)	4.5 (4.1–5.0)	4.4 (4.0–4.9)	0.15
Chest X-ray (CXR)			
Normal	46 (14%)	96 (11%)	0.25

Continued

Table 1 Continued

	Smokers n=336	Never smokers n=837	P value
Alveolar/interstitial infiltrates	281 (85%)	727 (88%)	
Pleural effusion	5 (1%)	6 (1%)	
CT chest			
Normal	0	3 (2%)	0.19
Alveolar/interstitial infiltrates	52 (96%)	133 (97%)	
Pleural effusion	2 (4%)	1 (1%)	

ALC, Absolute lymphocyte count; ANC, Absolute neutrophil count; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CT, Computed tomography; HIV, Human immunodeficiency virus; IQR, Interquartile range.

(1.2 mg/dL vs 1.0 mg/dL, $p < 0.001$) and higher median mean corpuscular volume (89.16 fL vs 88 fL, $p = 0.008$) compared with non-smokers. There were no differences between the two groups with regards to chest X-ray or CT findings (table 1).

Evaluating the in-patient treatment, smokers were more likely to develop critical illness requiring mechanical ventilation (47% vs 37% $p = 0.005$). Use of hydroxychloroquine, antiretrovirals, systemic steroids was similar between the two group whereas tocilizumab use was higher in non-smokers. Median survival was 14 days (95% CI 12 to 17 days) in smokers and 16 days (95% CI 14 to 18 days) in non-smokers, which was statistically significant (table 2; figure 1). Overall mortality was 31% (259/837) in non-smoker group and 39% (131/336) in smoker group.

Of the 336 smokers, 172 (51.2%) were past smokers and 164 (48.8%) were current smokers. Univariate Cox model for survival analysis by smoking status showed that smokers had higher risk of death compared with non-smokers (HR 1.34, 95% CI 1.08 to 1.66; $p = 0.006$). When the analysis was repeated with smokers subdivided into current smokers and past smokers, only current smokers had higher risk of death than non-smokers (HR 1.62, 95% CI 1.22 to 2.13; $p = 0.001$). Survival for the past smokers was similar to non-smokers (HR 1.15, 95% CI 0.87 to 1.51, $p = 0.32$).

In the Cox multivariate regression model, stepwise backward selection was used with $p > 0.1$ for removal. Only those variables are presented that were not removed during the selection process. The smoking status was removed due to not being significant. Significant effects

Table 2 Comparison of the various in-hospital therapies and outcomes between smokers and never smokers

	Smokers n=336	Never smokers n=837	P value
Oxygen therapy			
None	36 (11%)	126 (15%)	
Low-flow oxygen	102 (30%)	278 (33%)	
High-flow oxygen	39 (12%)	126 (15%)	
Invasive mechanical ventilation	159 (47%)	307 (37%)	0.005
Medications			
Hydroxychloroquine	243 (72%)	624 (75%)	0.43
Antiretrovirals	38 (11%)	81 (10%)	0.68
Steroids	114 (34%)	304 (36%)	0.44
Tocilizumab	17 (5%)	85 (10%)	0.005
Severity of illness			
Mild (0)	6 (2%)	11 (1%)	
Moderate (1)	30 (9%)	115 (14%)	
Severe (2)	141 (42%)	404 (48%)	
Critical (3)	159 (47%)	307 (37%)	0.003
Survival time (days)	Median survival=14 95% CI 12 to 17 days	Median survival=16 95% CI 14 to 18 days	0.005
Mortality	131/336 (39%)	259/837 (31%)	0.009

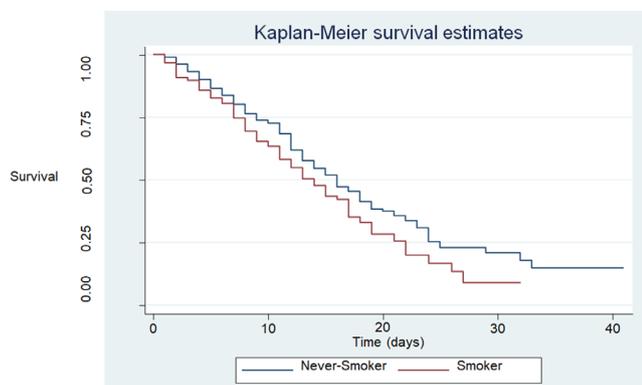


Figure 1 Kaplan-Meier survival curve in never smokers (blue line) and smokers (red line; $p=0.006$).

were observed for female sex (HR 0.67, 95% CI 0.53 to 0.84, $p=0.001$) old age (HR 1.02, 95% CI 1.02 to 1.03, $p<0.001$), high serum LDH (HR 1.00, 95% CI 1.00 to 1.00, $p<0.001$), and systemic steroid use (HR 0.62, 95% CI 0.49 to 0.77, $p<0.001$; [table 3](#)).

Role of systemic steroids

A total of 418 patients received systemic steroids. Of these, 235 patients were critically ill, 72 had severe illness, 84 had moderate illness and 35 patients had mild COVID-19 related illness. To compare the survival times, log-rank test was used for severely ill and critically ill patients. Additionally, the Kaplan-Meier estimates were plotted. No significant differences in outcomes were observed for severely ill patients ($p=0.29$). In critically ill patients, analysis revealed that median survival time was 13 days (95% CI 12 to 14 days) for patients who received systemic steroids compared with 6 days (95% CI 5 to 7 days) for those who did not ($p<0.0001$; [figure 2](#)).

DISCUSSION

Our study evaluated the patients that were admitted to our institution during the heart of the COVID-19 pandemic. We looked at various data points and how they correlated to the severity of COVID-19 infection. We found a direct relationship between smoking and severity of illness as well as mortality. When we subdivided smokers into current smokers and past smokers, we noticed that only current smokers had higher mortality compared with never smokers. This finding is in contrast

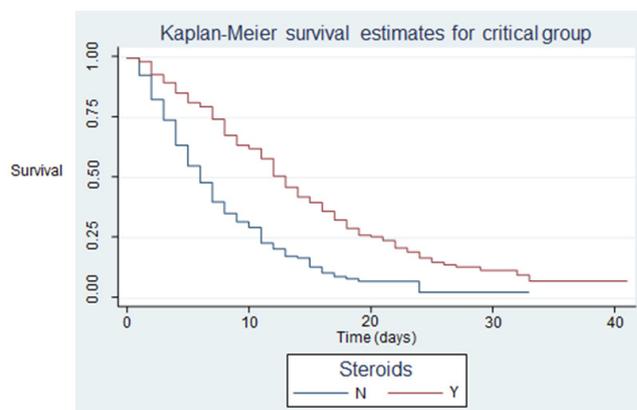


Figure 2 Kaplan-Meier survival curve in critically ill patients who received systemic steroids (Steroids=Y), and those who did not (steroids=N; $p<0.0001$).

with the recently published literature that showed significant upregulation of pulmonary ACE2 gene expression in both current and past smokers. The study suggested this upregulation increases risk of viral binding and entry of the virus into the lungs of both current and past smokers.⁹

Another significant finding of our study was that 28.6% of our patients had smoked at some point in their lives. This number is higher than what has been reported in the recent literature. In two meta-analyses, pooled prevalence of smokers in hospitalised patients was 7.6% (3.8%–12.4%) and 6.5% (1.4%–12.6%).^{15 16} From calendar year 2012 to year 2016, New York City has seen a significant decrease in the percentage of adults who smoke.¹⁰ This reduction has been attributed to comprehensive strategies that include media campaigns, smoke free air policies and increased access to cessation resources. Nonetheless, 13.1% of the adult living in New York City still smoke cigarettes.¹⁰ In our study, 164 patients (13.9%) were current smokers which correlates with the prevalence data of the New York City. Given similar rates of current smokers in our cohort of patients compared with that of the general population of New York City, the current study cohort is representative.

Survival analysis further revealed that women were at lower risk of mortality than men (HR of 0.67), which is consistent with recently published data.¹⁷ While exact mechanism that confers protection to females is not known, a study showed that the circulating ACE2 levels are higher in men than in women.¹⁸ These findings may suggest why men are at higher risk of developing serious COVID-19 illness. Increased age and serum LDH levels were also shown to be independently associated with survival. In addition, our data showed that patients who received systemic steroids were more likely to survive. On further analysis, this finding was not significant for severely ill patients. Critically ill patients showed significant survival advantage with use of systemic steroids. Systemic steroids in COVID-19 have been much of controversy. Earlier guidelines issued by WHO on 13

Table 3 Cox model for survival

Multivariate Cox model for survival		
Parameter	HR (95% CI for HR)	P value
Female gender	0.67 (0.53 to 0.84)	0.001
Age	1.02 (1.02 to 1.03)	<0.001
Admission LDH	1.00 (1.00 to 1.00)	<0.001
Systemic steroids	0.62 (0.49 to 0.77)	<0.001

LDH, lactate dehydrogenase.



March 2020 advised to avoid routine use system steroids for treatment of viral pneumonia.¹⁹ A literature review by Russel *et al*²⁰ went even further and stated that not only that the evidence does not support any benefit but there may even be harm if steroids are used in patients with COVID-19. Wu *et al*¹³ subsequently published their findings in a subgroup of patients with COVID-19 who developed ARDS. Their study showed that patients who received methylprednisolone were more likely to survive compared with those who did not. This study was one of the key considerations when our institutional protocol suggested the use of systemic steroids in select subgroup of patients hospitalised with COVID-19. Our results confirm the findings by Wu *et al*¹³ in suggesting benefits of systemic steroids use in critically ill patients. Our study results are also in line with recovery trial findings that showed that use of dexamethasone resulted in lower 28-day mortality (29.3% vs 41.4%; 95% CI 0.51 to 0.81) among those patients with COVID-19 illness who required mechanical ventilation. In addition, recovery trial also found a mortality benefit in patients with COVID-19 who were receiving oxygen therapy (23.3% vs 26.2%; 95% CI 0.72 to 0.94), which our study did not show.¹²

Our study has several limitations. First, this is a single centre, retrospective study, and therefore at risk of selection bias. Second, as this study includes patients that were admitted during the COVID-19 crisis, many of whom were seriously ill to provide detailed history, data were limited with regards to pack year smoking as well as how long ago past smokers quit smoking. Third, we did not account for other inhaled recreational agents such as marijuana. Finally, our study tested multiple hypotheses, yet not all confounders may be accounted for in multivariate models. Our findings need further confirmation in a larger prospective cohort.

CONCLUSION

Our study findings suggest that smoking is associated with higher likelihood of developing critical illness and higher likelihood of death in patients hospitalised with COVID-19 illness. Use of systemic steroids in critically ill patients was independently associated with improved survival.

Acknowledgements The authors want to thank Magdalena Murawska for performing the statistical analysis.

Contributors All authors have made substantial contributions to all of the following: (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study was approved by the institutional review board at Bronxcare Health System under an expedited review in the setting of a global pandemic (IRB # 06 11 20 09). Need for consent was waived due to retrospective nature of the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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ORCID iD

Muhammad Adrish <http://orcid.org/0000-0002-5553-6182>

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