

# Association of Smoking Status with Outcomes in Hospitalized COVID-19 Patients

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## Research

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# Abstract

## Introduction:

Smoking causes inflammation of the lung epithelium by releasing cytokines and impairing muco-ciliary 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 hospitalized with COVID-19 from March 09 to May 18, 2020.

**Results:** 1173 patients met the study criteria. 837 patients never smoked and 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 COPD (19% vs. 6%,  $p<0.001$ ), human immunodeficiency virus 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%,  $p=0.037$ ), and end-stage renal disease (10% vs. 6%,  $p=0.009$ ) compared to non-smokers. 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 smokers only current smokers had higher risk of death compared to never-smokers (HR 1.61, 95% confidence interval 1.22–2.12,  $p<0.001$ ). In the multivariate approach Cox model for the survival, female sex, age, LDH and systemic steroid use were associated with overall survival.

**Conclusion:** In our large single center retrospective database of patients hospitalized 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.<sup>1</sup> The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), which belongs to the

subgenus Sarbecovirus (Beta-CoV lineage B), Orthocoronavirinae subfamily.<sup>2</sup> 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.<sup>3</sup> Symptoms vary significantly from 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, etc.<sup>4,5</sup> 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<sup>1</sup> showed that current and former smokers were more likely to present with severe coronavirus disease 2019 (COVID-19). In another small study, Liu et al showed that smoking history was associated with progression of COVID-19.<sup>5</sup> Contrary to these findings, study by Huang et al,

showed that current smoking history is not associated with need for ICU care.<sup>6</sup> Similar findings were observed by subsequent larger observational studies.<sup>7,8</sup>

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 to never-smokers. These findings suggested that ever smokers have increased risk of viral binding and entry into the lungs.<sup>9</sup> 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 residents' smoke.<sup>10</sup> Bronx was also one of the hardest hit boroughs of the New York City during the COVID-19 pandemic.<sup>11</sup> In this retrospective study, we aimed to analyze the effects of smoking habits in the outcomes of patients hospitalized with COVID-19 illness.

## Methods

### Study Setting

We conducted this study at BronxCare Health System (BCHS), the largest voluntary, not-for-profit health and teaching hospital system, serving the south and central Bronx in the New York City. We retrospectively analyzed all consecutively hospitalized adults with COVID-19 from March 09 to May 18, 2020. A diagnosis of COVID-19 was established when a patient tested positive for the virus SARS-CoV-2 from the polymerase chain reaction (PCR) analysis of nasopharyngeal swab specimens at any point during their hospitalization. This study was approved by the institutional review board at BCHS 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.

### Participants and eligibility criteria

We included adult patients with known smoking status who were hospitalized with COVID-19 for whom severity of illness could be established and had final disposition status at the time of the study. 1336 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 because their final outcome was not known for survival to hospital discharge analysis. 17 patients were excluded because the disease severity could not be established due to missing data elements (Fig. 1). 1173 (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.

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,

medication administration history, and ventilator requirement data.

Study outcomes were defined as severity of illness and mortality.

## Severity of illness

- Hypoxia was defined as 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 chi-square test for comparing categorical variables between smokers and non-smokers. Because the normality assumption was violated for continuous variables, the nonparametric 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 modeling survival times with all baseline characteristics. 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 version 14.2.

## Results

1173 patients met the study criteria and were included in final analysis (Fig. 1). 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 (BMI). Males and African Americans were more likely to be smokers. Smokers had higher incidence of COPD (19% vs. 6%,  $p < 0.001$ ), human immunodeficiency virus 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%,  $p = 0.037$ ), and end-stage renal disease (10% vs. 6%,  $p = 0.009$ ) compared to non-smokers (Table 1). Admission D-dimer, lactate dehydrogenase (LDH), absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and C-reactive protein (CRP), ferritin, serum lactate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, serum albumin, hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count, serum sodium and serum potassium levels were similar between the two groups. Smokers had higher serum creatinine

(1.2 mg/dl vs. 1.0 mg/dl,  $p = 0.0144$ ) and higher mean corpuscular volume (89.16 vs 88,  $p = 0.008$ ) compared to non-smokers. There was no difference between the two groups with regards to chest x-ray or computed tomography findings.

Table 1  
Baseline demographics of smokers and never-smokers. N = number of patients.

	<b>Smokers N = 336</b>	<b>Never-Smokers N = 837</b>	<b>P value</b>
Age, years – median (IQR)	64 (54–73)	62 (52–73)	0.296
Sex - no (%)	87 (26%)	366 (44%)	< 0.001
Female	249 (74%)	471 (56%)	
Male			
Ethnicity – no (%)	183 (54%)	548 (66%)	< 0.001
Hispanic	114 (34%)	206 (25%)	
Black 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)	0.693
Comorbidities – no (%)	213 (63.4%)	524 (63%)	0.819
Hypertension Diabetes mellitus HIV infection/AIDS	158 (47%)	377 (45%)	0.683
Asthma COPD	37 (11%)	39 (5%)	< 0.001
Chronic Liver Disease	52 (16%)	111 (13%)	
Any Cancer Congestive heart failure Coronary artery disease Chronic kidney disease	64 (19%)	49 (6%)	< 0.001
ESRD	5 (1.5%)	6 (1%)	
	36 (11%)	50 (6%)	0.381
	50 (15%)	66 (8%)	0.005
	49 (15%)	78 (9%)	< 0.001
	38 (11%)	63 (8%)	
	35 (10%)	64 (6%)	0.027
			0.037
			0.009

\*Mean and SD not provided since normality assumption violated

Abbreviations: COPD: chronic obstructive pulmonary disease, ESRD: end stage renal disease, k/ul: cubic milimter, fl; femtoliter, g/dl; gram per deci liter mEq/L: miliequivalents per liter, mg/dl: milligram per deciliter, mg/L: milligram per liter, mmol/l: milli mole per liter, ng/ml: nannogram per milliliter, pg; pico gram, SD: standard deviation, unit/L: unit per liter

	Smokers N = 336	Never-Smokers N = 837	P value
<b>Initial laboratory tests – median (IQR)*</b>			
Absolute neutrophil count (ANC) (k/ul)	5.7 (3.7–8)	6.0 (4.1–8.3)	0.256
Absolute lymphocyte count (ALC) (k/ul)	0.8 (0.5–1.3)	0.9 (0.6–1.2)	0.692
ANC/ALC ratio	6.6 (4.0–11.6)	6.8 (4.3–11.4)	0.488
D-dimer (ng/ml)	536 (317–1025)	533 (304–1254)	0.945
Lactate Dehydrogenase (u/L)	490 (308–741)	483 (350–690)	0.633
C-reactive protein (mg/L)	104.3 (46.6–181.4)	117.65 (62.42–198.70)	0.232
Ferritin (ng/ml)	752.6 (328.8–1466.5)	700.1 (364.6–1380.5)	0.402
Lactate (mmoles/L)	1.8 (1.3–2.55)	1.8 (1.3–2.5)	0.404
Creatinine (mg/dl)	1.2 (0.9–2.07)	1.0 (0.8–1.6)	<b>&lt; 0.001</b>
Alanine Aminotransferase (unit/L)	29 (18–49)	29 (18–48)	0.986
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)	0.668
Serum Albumin (g/dl)	3.6 (3.2–4)	3.6 (3.3–3.9)	0.667
Hemoglobin (g/dl)	13.2 (11.7–14.6)	13.2 (11.8–14.5)	0.893
White blood cell (k/ul)	7.3 (5.3–9.8)	7.5 (5.5–10.2)	0.321
Mean corpuscular volume (fL)	89.15 (84.9–93.1)	88 (83.7–91.7)	<b>0.008</b>
Mean corpuscular hemoglobin (pg)	33.4 (32.6–34.0)	33.3 (32.5–34.0)	0.243

\*Mean and SD not provided since normality assumption violated

Abbreviations: COPD: chronic obstructive pulmonary disease, ESRD: end stage renal disease, k/ul: cubic milimter, fl; femtoliter, g/dl; gram per deci liter mEq/L: miliequivalents per liter, mg/dl: milligram per deciliter, mg/L: milligram per liter, mmol/l: milli mole per liter, ng/ml: nannogram per milliliter, pg; pico gram, SD: standard deviation, unit/L: unit per liter

	<b>Smokers</b> <b>N = 336</b>	<b>Never-Smokers</b> <b>N = 837</b>	<b>P value</b>
Serum Sodium (mEq/L)	136 (133–139)	137 (133–139)	0.376
Serum Potassium (mEq/L)	4.5 (4.1–5.0)	4.4 (4.0–4.9)	0.150
Chest x-ray (CXR)	46 (14%)	96 (11%)	0.248
Normal Alveolar/interstitial infiltrates	281 (85%)	727 (88%)	
Pleural effusion	5 (1%)	6 (1%)	
CT chest	0	3(2%)	0.186
Normal Alveolar/interstitial infiltrates	52 (96%)	133 (97%)	
Pleural effusion	2 (4%)	1 (1%)	
*Mean and SD not provided since normality assumption violated			
Abbreviations: COPD: chronic obstructive pulmonary disease, ESRD: end stage renal disease, k/ul: cubic milimter, fl; femtoliter, g/dl; gram per deci liter mEq/L: miliequivalents per liter, mg/dl: milligram per deciliter, mg/L: milligram per liter, mmol/l: milli mole per liter, ng/ml: nannogram per milliliter, pg; pico gram, SD: standard deviation, unit/L: unit per liter			

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, anti-retrovirals, systemic steroids was similar between the two group whereas Tocilizumab use was higher in non-smokers.

Median survival was 14 days (95% confidence interval 12–17 days) in smokers and 16 days (95% confidence interval 14–18 days) in non-smokers, which was statistically significant (Table 2).



Table 2

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

	<b>Smokers</b> <b>N = 336</b>	<b>Never-Smokers</b> <b>N = 837</b>	<b>P value</b>
Oxygen Therapy	36 (11%)	126 (15%)	0.005
None	102 (30%)	278 (33%)	
Low flow oxygen High flow oxygen	39 (12%)	126 (15%)	
Invasive mechanical ventilation	159 (47%)	307 (37%)	
Medications	243 (72%)	624 (75%)	0.432
Hydroxychloroquine Anti-retrovirals	38(11%)	81 (10%)	0.677
Steroids	114 (34%)	304 (36%)	0.439
Tocilizumab	17 (5%)	85 (10%)	0.005
Severity of illness	6 (2%)	11 (1%)	0.003
Mild (0)	30 (9%)	115 (14%)	
Moderate (1)	141 (42%)	404 (48%)	
Severe (2)	159 (47%)	307 (37%)	
Critical (3)			
Survival time (days)	Median survival = 14  95%CI = 12–17 days	Median survival = 16  95%CI = 14–18 days	0.0050

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 hazard ratio for smokers was 1.34 suggesting that this group have the risk of death 34% higher than non-smokers (Fig. 2). When the analysis was repeated with smokers subdivided into current smokers and past smokers, hazard ratio for smokers was 1.615 suggesting that this group have the risk of death 61.5% higher than non-smokers.

Survival for the past smokers was similar to non-smokers (HR 1.14, 95% confidence interval 0.8739–1.5125) (Fig. 3) (Table 3).

Table 3  
Univariate Cox Model for Smoking and Survival

Risk Factors	Hazard Ratio (HR) (95% CI for HR)	p value
Current and Past Smoker	1.34 (1.08–1.66)	0.006
Current Smoker	1.61 (1.22–2.12)	0.001
Past Smoker	1.14 (0.87–1.51)	0.319
Abbreviations: CI; confidence interval, HR; hazard ratio		

In the multivariate approach Cox model for the survival, the significant effects were observed for female sex, age, LDH and systemic steroid use. HR for age was equal 1.02, which indicated the risk of death increasing by 2% with every additional year of age of the patient at baseline. HR for systemic steroids was equal to 0.42, which indicates the risk of death smaller by 58% for patients taking systemic steroids. HR for female gender was equal 0.75, which indicates the risk of death smaller by 25%. HR for LDH was equal 1.0005 that indicated the increase of 0.05% in the risk of death by every additional unit of LDH (Table 4).

Table 4  
Multivariate Cox Model for Survival

Parameter	Hazard Ratio (HR) (95% CI for HR)	p value
Female Gender	0.67 (0.53–0.84)	0.001
Age	1.02 (1.02–1.03)	< 0.001
Admission LDH	1.00 (1.00–1.00)	< 0.001
Systemic Steroids	0.62 (0.49–0.77)	< 0.001
Abbreviations: CI; confidence interval, HR; hazard ratio, LDH; lactate dehydrogenase		

## 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  $p = 0.2903$  (Fig. 4). In critically ill patients, analysis revealed that median survival time was 13 days (95% confidence interval 12–14 days) for patients who received systemic steroids compared to 6 days (95% confidence interval 5–7 days) for those who did not ( $p < 0.0001$ ) (Fig. 5).

## 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. Our data suggests that patients who ever smoked in their lives, had risk of death 34% higher compared to never-smokers. This translated to median survival time of 14 days in smokers, which was statistically lower than never-smokers who had median survival of 16 days. We then subdivided smokers into current smokers and past smokers; we noticed that risk of death in current smokers was 61% higher compared to never smokers. When past smokers were compared with never smokers, we did not find any statistical increase in risk of death. This finding is in contrast with the recently published literature that showed significant up-regulation of pulmonary ACE2 gene expression in both current and past smokers. The study suggested this up-regulation increased risk of viral binding and entry of the virus into the lungs of both current and past smokers.<sup>9</sup>

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 hospitalized patients was 7.6% (3.8–12.4%) and 6.5% (1.4% – 12.6%)<sup>12, 13</sup> From calendar year 2012 to year 2016, New York City has seen a significant decrease in the percentage of adults who smoke.<sup>10</sup> 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.<sup>10</sup> In our study, 164 patients (13.9%) were current smokers which correlates with the prevalence data of the New York City. This finding may suggest that risk of getting hospitalized with COVID-19 illness is similar between smokers and general population.

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.<sup>14</sup> 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.<sup>15</sup> 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.

Upon 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. Guidelines issued by World Health Organization on March 13th 2020 had advised to avoid routine use system steroids for treatment of viral pneumonia.<sup>16</sup> A literature review by Russel et al. 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 COVID-19 patients.<sup>17</sup> Wu et al. subsequently published their findings in a subgroup of COVID-19 patients who developed ARDS.<sup>18</sup> Their study showed that patients who

received methylprednisolone were more likely to survive compared to 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 hospitalized with COVID-19. Our results confirm the findings by Wu et al. in suggesting benefits of systemic steroids use in critically ill patients.

Our study has several limitations. First, this is a single center, 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 was 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. 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 hospitalized with COVID-19 illness. Use of systemic steroids in critically ill patients was independently associated with improved survival.

## Abbreviations

ACE

Angiotensin Converting Enzyme

ALC

Absolute Lymphocyte Count

ALT

alanine aminotransferase

ANC

Absolute Neutrophil Count

ARDS

Acute Respiratory Distress Syndrome

AST

aspartate aminotransferase (AST)

BCHS

BronxCare Health System

BMI

Body Mass Index

COPD

Chronic Obstructive Pulmonary Disease

CoV

Coronavirus

COVID  
Coronavirus Disease  
CRP  
C-reactive protein  
HR  
Hazard Ratio  
ICU  
Intensive Care Unit  
IRB  
Institutional Review Board  
LDH  
Lactate Dehydrogenase  
MERS  
Middle East Respiratory Syndrome  
PCR  
polymerase chain reaction  
RSV  
Respiratory Synticial Virus  
SARS-COV-2  
Severe Acute Respiratory Syndrome Coronavirus 2

## **Declarations**

### **Ethics approval and consent to participate:**

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.

### **Availability of data and material:**

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

### **Competing interests:**

The authors declare no financial and non-financial competing interests.

### **Funding:**

The authors received no specific funding for this work.

## Author contributions:

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.

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## Consent to publication:

Not applicable.

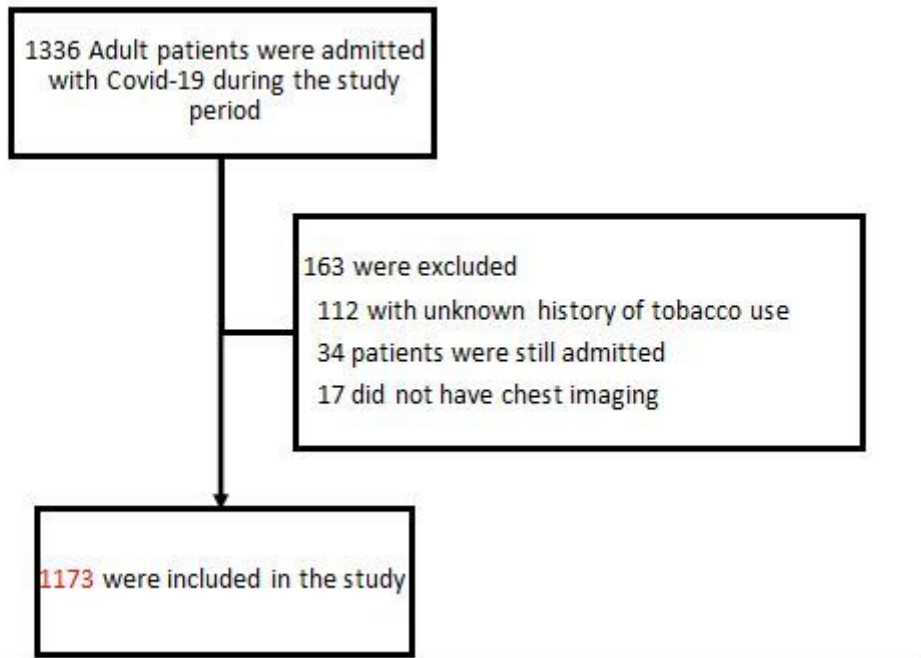
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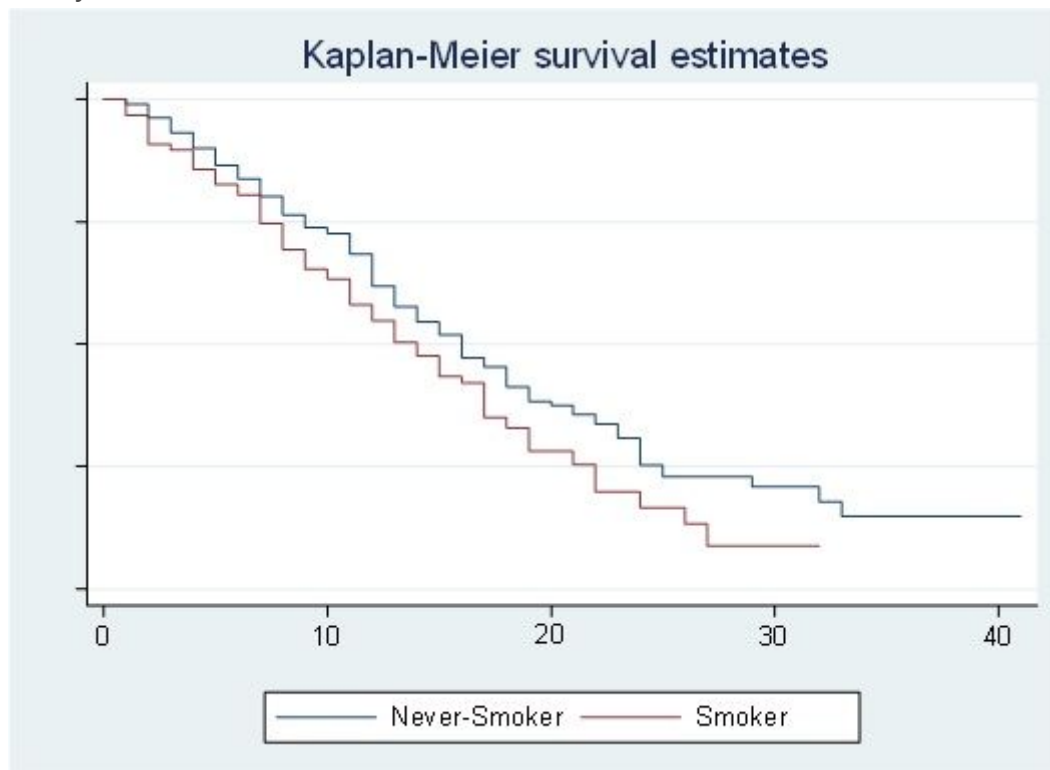
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## Figures



**Figure 1**

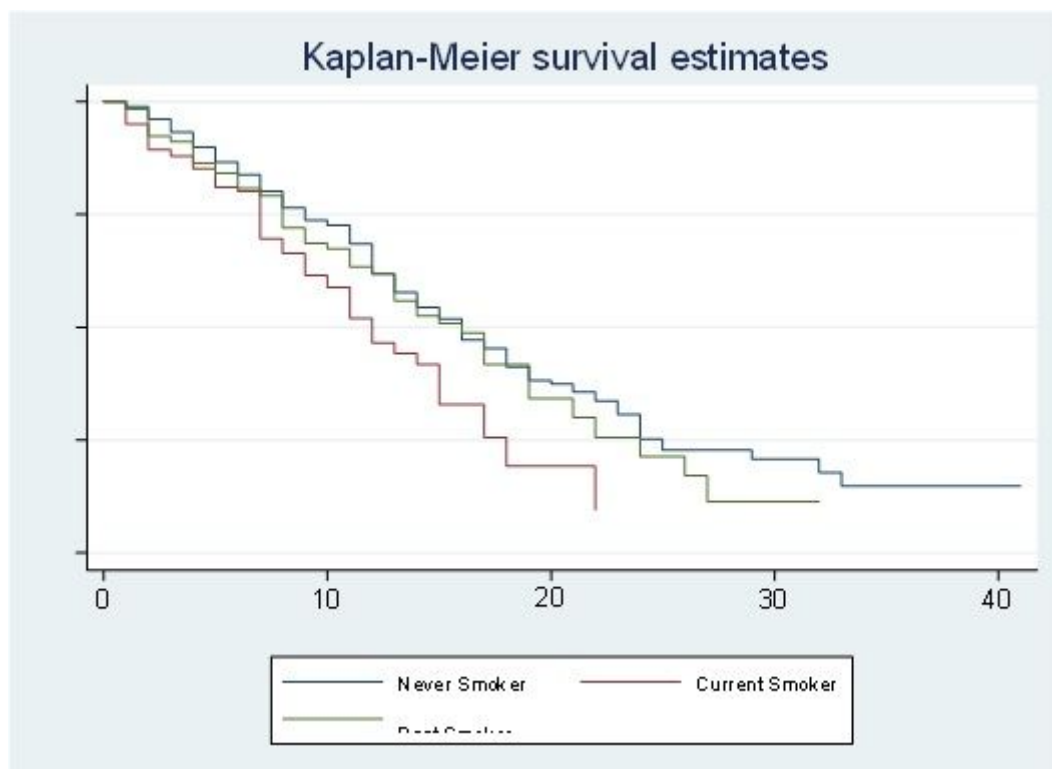
Study Cohort



**Figure 2**

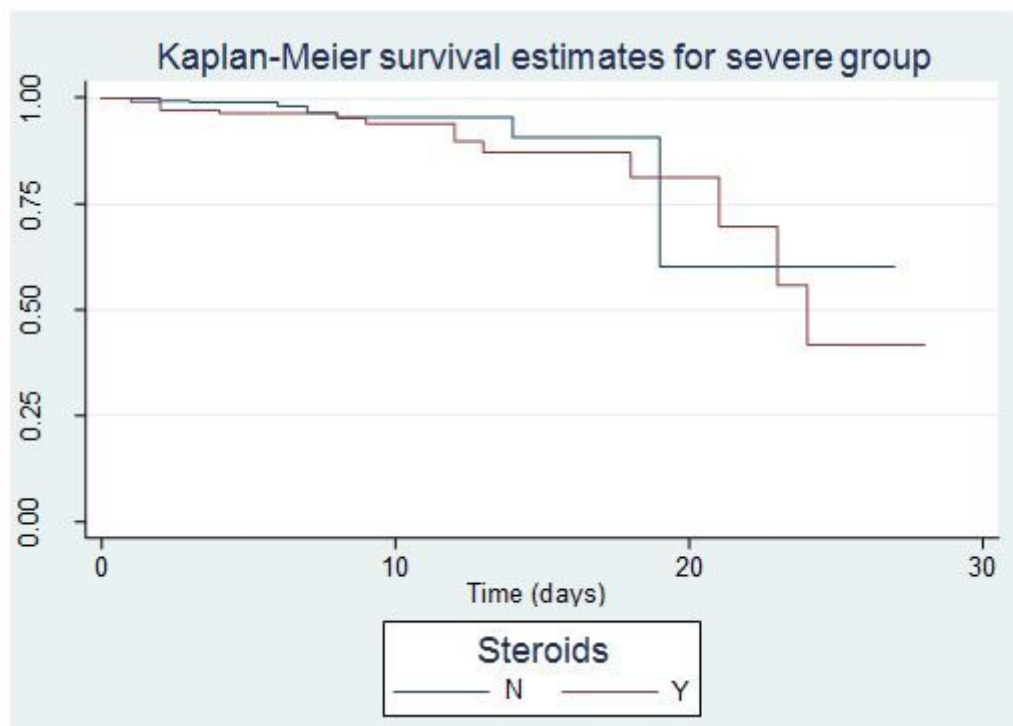
Kaplan-Meier survival curve in never-smokers (blue line) and smokers (red line)





**Figure 3**

Kaplan-Meier survival curve in current smokers (red line), past smokers (green line) and never-smokers (blue line)



**Figure 4**

Kaplan-Meier survival curve in severely ill patients who received systemic steroids (Steroids = Y), and those who did not (Steroids = N)

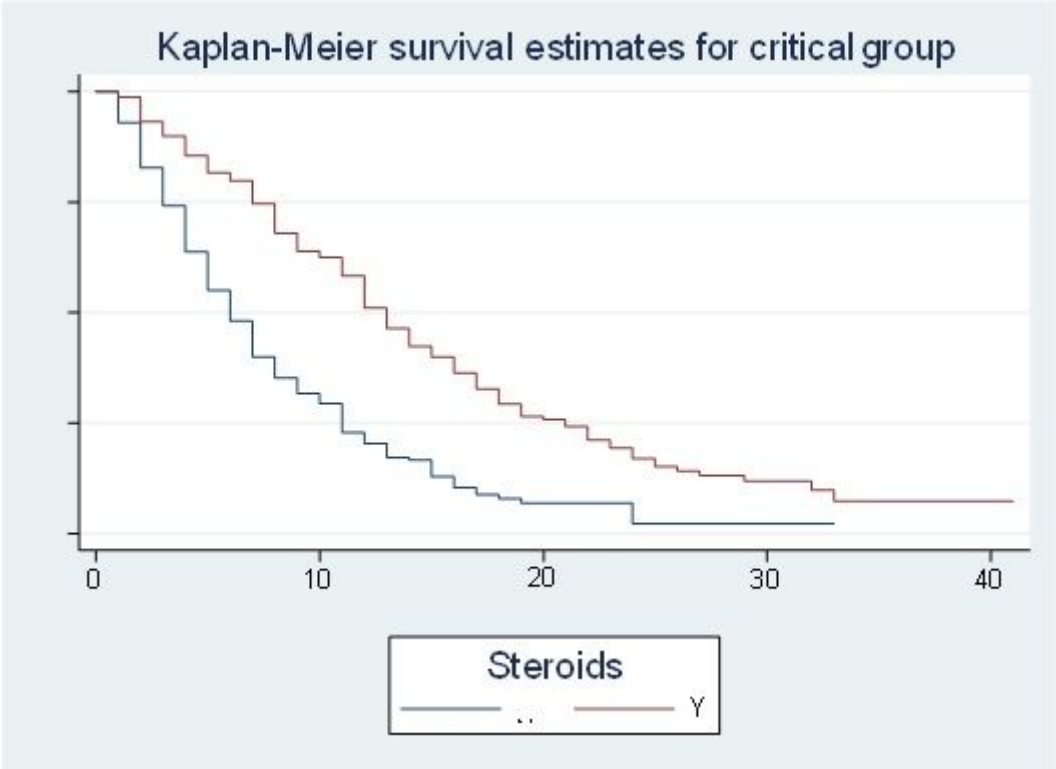


Figure 5

Kaplan-Meier survival curve in critically ill patients who received systemic steroids (Steroids = Y), and those who did not (Steroids = N)