ORIGINAL ARTICLE

Clinical Profile and Outcomes of COVID-19 Positive Patients with Chronic Obstructive Pulmonary Disease (COPD) in a Tertiary Government COVID-19 Referral Center

Mary Bianca Doreen F. Ditching, MD and Joel M. Santiaguel, MD, MOH

Division of Pulmonary Medicine, Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Introduction. It is anticipated that Chronic Obstructive Pulmonary Disease (COPD) has greater risk in acquiring COVID-19 infection and poorer outcome. However, current worldwide data are conflicting.

Objectives. This study primarily aims to compare the outcomes of COVID-19 patients with COPD and those without COPD in terms of length of hospital stay (LOS), recovery or mortality, treatment received, and predictors of mortality.

Methods. This is a retrospective cohort chart review of 1,017 admitted adult COVID-19 patients from July to December 2020. Age, gender, smoking status, current control and medications for COPD, COVID-19 severity, symptoms, treatment, and outcomes of the two study groups were compared.

Results. Prevalence rate of COPD was 3.8%. COVID-19 patients with COPD were older (median age of 69 vs 54, p<0.001), male (87% vs 50%, p<0.001), hypertensive (72% vs 48%, p=0.004), and with tuberculosis (31% vs 11%, p=0.002). COVID-19 patients with COPD more commonly needed oxygen therapy, High Flow Nasal Cannula, Mechanical Ventilation, Tocilizumab, Convalescent Plasma Therapy and Dexamethasone, and had longer LOS. Significant risk factors for mortality are malignancy, investigational therapies, smoking, and older age. There was no difference in survival rates between the two groups.

Conclusion. COPD increases the risk for severe COVID-19 and lengthens LOS.

Keywords: COVID 19, COPD, Chronic Obstructive Pulmonary Disease, mortality, predictors

BACKGROUND

The coronavirus disease 2019 (COVID-19) was first noted on December 2019 due to an outbreak in Wuhan, China and it has spread worldwide causing a pandemic virtually affecting almost all countries. It is an acute respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Presenting manifestations as well as signs and symptoms of the disease are heterogenous and severity varies greatly in each individual.

Several studies have tackled various risk factors that could possibly affect the severity of COVID-19 infection in patients. Risk factors include age, high LDL level, and high D-dimer levels as well as presence of comorbidity.[2] According to a study by Guan et al., 20-51% of patients admitted with COVID 19 infection have at least one of the following co-morbidity namely: diabetes (10-20%), hypertension (10-15%),

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Corresponding author: Mary Bianca Doreen F. Ditching, MD
Division of Pulmonary Medicine
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: biancaditchingmd@gmail.com
ORCiD: https://orcid.org/0009-0003-7376-0246

and cardiovascular and cerebrovascular disease (7-40%).[3] Co-morbidities were also seen more frequently in severe cases of COVID-19. Additionally, poorer prognosis is seen in patients with diabetes, hypertension, respiratory disease, cardiac disease, pregnancy, renal disease, and malignancy. They are more predisposed to adverse clinical outcomes especially if with COVID-19.[3]

It is anticipated that patients with pre-existing lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) would be at greater risk in acquiring COVID-19 infection. Respiratory diseases are highly prevalent worldwide and reports indicate that about 65 million people suffer from COPD and 334 million people suffer from asthma.[4] However, the incidence of COVID-19 in the said population is frequently lower than the prevalence of these conditions in the general population.[1] It has been reported that the percentage of patients with COVID-19 infection with COPD is at 1.5-5% and those with asthma at 0-12.5%.[1]

The Philippines has 3,667,542 COVID-19 cases as of March 2022 and is 26th in the highest census worldwide. The Philippine General Hospital has been designated as a COVID-19 referral center since March 24, 2020 and has catered to at least 9,264 patients with COVID-19. To date, there is no local data or published studies regarding clinical profiles and outcomes of COVID-19 positive patients with COPD. The results of this study will help in further understanding the relationship of COVID-19 and Chronic Obstructive Pulmonary Disease (COPD).

OBJECTIVES

General Objectives

To compare outcomes between patients with pre-existing Chronic Obstructive Pulmonary Disease (COPD) infected with COVID-19 versus non-COPD patients infected with COVID 19

Specific Objectives

1. To determine the epidemiology of COPD patients infected with COVID-19 based on age, sex, current COPD control, COVID-19 disease severity, COVID-19 symptoms, treatment, and outcomes.
2. To determine the differences in outcomes in terms of length of hospital stay and mortality between COPD patients infected with COVID-19 versus non-COPD patents infected with COVID-19.

METHODS

Setting and Study Design

This retrospective cohort study was conducted in a COVID-19 national referral center and tertiary government hospital from July to December 2020. The study commenced after being approved by the local ethics committee.

Study Population

The study reviewed the charts of patients aged 19 years and above admitted for COVID-19 infection diagnosed with COVID-19 Real Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) from July 2020 to December 2020. Patients were excluded in the study if: (1) Patients are clinically suspected with COVID-19 with no positive RT-PCR results; (2) Patients with incomplete or unavailable medical records (Figure 1).

Data Collection Procedure

All admitted adult COVID-19 patients in the Philippine General Hospital were included in the study. Gender, age, smoking status, COVID-19 symptoms, status, treatment and final management outcome, improved vs deceased, were obtained and recorded. For those who have concomitant COPD, information about the current control, medications used, and compliance were also extracted from patient medical records.

The diagnosis of COPD was based on either the physician's assessment, prior COPD (clinically diagnosed and/or laboratory confirmed to have Chronic Obstructive Pulmonary Disease with or without treatment for at least six months), history of progressive and persistent dyspnea, and no diagnostics such as spirometry were used.

A data collection form via Microsoft Excel for ease of documentation was used to collect the necessary variables and outcomes needed in the study. The said data collection form was transcribed into the primary investigator's laptop which is password protected. Only the investigator and research assistant were involved in reviewing the charts. All data was kept anonymous and no identifying codes that could link the data to the subject was made. In cases of incomplete or missing data, these were not included in the analysis.

All data transcribed were secured from the primary investigators' laptop to a password-protected hard drive for safekeeping and was only accessible to the study team. This was kept in a secure location within the study site and it will

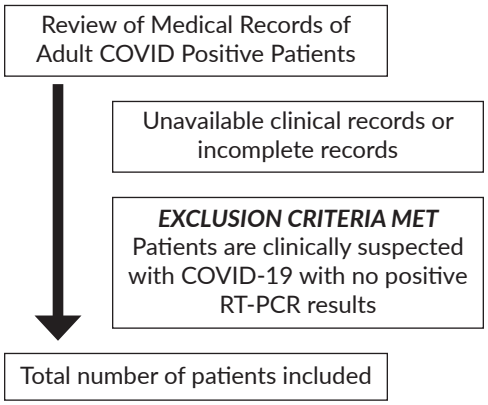

Figure 1. Flow diagram of patients included and excluded from the study.

be kept for a maximum of ten years after which it will be destroyed. The files will be deleted from the system and the hard drive used to store the data will be reformatted. All data transcribed were only shared with the statistician through secure means. Collection of data commenced last May 28, 2021 with approval from the Ethics Board.

Statistical Analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the patients. Categorical variables were presented as frequency and proportion. Shapiro-Wilk was used to determine the normality distribution while Levene's was used to test the homogeneity of variance of continuous variables. Skewed continuous quantitative data was reported as median and interquartile range (IQR). Statistical significance of differences between groups (with and without COPD) was evaluated by using the Mann-Whitney U test for skewed continuous data. Categorical variables were compared using Chi-square test. If the expected percentages in the cells are less than 5%, Fisher's Exact test was used. Two-sided p-value at P <0.05 were considered significant. Data were encoded using Microsoft Excel version 16.58 (Microsoft, USA) and STATA version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

RESULTS

A total of 1,503 charts were initially included in the study as these were those who were admitted from July to December 2020. Four hundred seventy-eight (478) were excluded due to incomplete data. One thousand twenty-five (1,025) charts were reviewed however there were seven patients who were re-admitted – six patients readmitted twice and one patient readmitted three times. Only the first admission was analyzed.

The 1,017 patients confirmed with COVID-19 were analyzed (Table 1). A total of 39 (3.8%) patients were diagnosed with COPD which is comparable to the prevalence of COPD in other studies which revealed a prevalence rate of 1.4-7.7%.[1,5-9] However, the study by Gasmi et al. described the prevalence of COPD in COVID-19 patients to be only 0.95%[10] while Bloom et al.'s analysis of data from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) WHO Clinical Characterization Protocol UK (CCP-UK) study described a prevalence as high as 15.6%.[11]

The COVID 19 patients with COPD were older (median age of 69 vs 54, p<0.001), male (87% vs 50%, p<0.001), with history of hypertension (72% vs 48%, p=0.004) and tuberculosis (31% vs 11%, p=0.002). All COPD patients were smokers – both previous and current (100% vs 24%, p<0.001) with a median pack year of 30 pack years. These are similar to the findings in a study done in Wuhan, China wherein clinical characteristics of COVID-19 patients with COPD were older (median age 71 years old) and male.[1] Similarly, findings by Calmes et al. also revealed that COVID-19 patients with COPD were more likely hypertensive.[8] All COPD patients were smokers with a median pack year of 30 which is an expected finding. It is a well-established fact that smoking is one of the risk factors for development of COPD. It is said that 15-50% of smokers develop COPD and 80-90% of COPD patients are smokers or former smokers.[5]

COPD patients with COVID 19 tend to have moderate to severe COVID as compared to those without COPD. Most of COVID-19 with COPD presented with cough (72% vs 53%, p=0.019). This finding is similar to several studies which state that COPD is a significant risk for severe COVID-19 infection to as high as a fivefold increase risk or 88% higher risk for severe disease.[1,4-6,10,12-15] Cough was also noted to be a frequent manifestation of COPD patients with COVID-19 which is not surprising since COPD patients suffer from chronic cough and sputum production. Fever, headache, cough, and myalgia were the most common presenting symptoms in patients with asthma and COPD with COVID-19[8] however, shortness of breath was the frequent symptom of COVID-19 patients with COPD[1].

All COPD patients were diagnosed via physician assessment and most of them were diagnosed within the last 6 months (64%). About 12% of the COPD population was under GOLD A Classification, 2% under GOLD B Classification, 14% under GOLD C Classification, and 11% under GOLD D Classification. COPD can be diagnosed based on history, symptomatology and spirometry to establish the presence of airflow limitation.[16] Spirometeric testing has been limited in the midst of the pandemic due to issues with aerosolization and spread of infection[16] hence diagnosis was based on physician assessment from history and physical examination.

Table 2 illustrates management and outcomes of patients based on COPD status. Patient with COPD more commonly needed oxygen therapy (80% vs 56%, p=0.004), High Flow Nasal Cannula (HFNC) use (44% vs 21%, p=0.001), Mechanical Ventilation (33% vs 20%, p=0.040), Tocilizumab (33% vs 19%, p=0.021), Convalescent Plasma Therapy (18% vs 6%, p=0.013), and Dexamethasone (82% vs 52%, p<0.001). The length of hospital stay of those with COPD was significantly longer with a median stay of 14 days as compared to those without COPD with median stay of 12 days. Median length of hospital stay for those with mild to moderate COVID is at 10 days while those with severe COVID-19 stayed for a median of 16 days and those with critical COVID at 13 days. However, there was insufficient evidence to distinguish a difference in the survival rates of those without COPD (79%) and those with COPD (69%). This finding is comparable to the study of Calmes et al. which showed that COPD was a predictor of death in the univariate analysis but not in the age and sex adjusted and multivariate analysis[8] and in the systematic review and meta-analysis done by Gerayeli et al. in which there is no sufficient evidence that

COPD is related to mortality after adjusting for age and sex[17]. However, this is a different finding from several studies wherein patients with COPD have an increased mortality rate (54-60%) as compared to patients without underlying respiratory conditions.[7,9,11,13-14] Differences in results may be due to difference in the population of the studies as well as prevalence of COPD in the study population.

About 218 (21.44%) patients died and mortality rates in the COPD group and non-COPD group were at 30.77% and 21.06%, respectively as shown in Table 3. A study done in Leige, Belgium also had similar outcomes where 34.8% of COVID-19 patients with COPD died.[8] Using the GOLD grade, in hospital mortality rate were as follows 8.33% for GOLD A, 50% for GOLD B, 28.57% for GOLD C and 54.55% for GOLD D patients.

Table 1. Characteristics of COVID-19 Patients, by COPD Status (n=1017)

	All (n=1017)	No COPD (n=978)	With COPD (n=39)	*p*-value
	Median (IQR); Frequency (%)			
Age, years	55 (40-65)	54 (40-64)	69 (62-77)	<.001*
<60	630 (61.95)	624 (63.8)	6 (15.38)	
≥60	387 (38.05)	354 (36.2)	33 (84.62)	
Sex				**<.001**†
Male	522 (51.33)	488 (49.9)	34 (87.18)	
Female	495 (48.67)	490 (50.1)	5 (12.82)	
Comorbidities				
Hypertension	500 (49.16)	472 (48.26)	28 (71.79)	**.004**†
Diabetes mellitus	283 (27.83)	271 (27.71)	12 (30.77)	.676†
Cardiovascular disease	104 (10.23)	97 (9.92)	7 (17.95)	.108‡
Chronic kidney disease	81 (7.96)	80 (8.18)	1 (2.56)	.359‡
Chronic liver disease	11 (1.08)	10 (1.02)	1 (2.56)	.351‡
Malignancy	80 (7.87)	77 (7.87)	3 (7.69)	.999‡
Asthma	95 (9.34)	93 (9.51)	2 (5.13)	.572‡
Past or present TB disease	128 (12.59)	116 (11.86)	12 (30.77)	**.002**‡
Smoking history				**<.001**‡
Never	741 (72.86)	741 (75.77)	0 (0)	
Previous	229 (22.52)	197 (20.14)	32 (82.05)	
Current	47 (4.62)	40 (4.09)	7 (17.95)	
Pack-years	10 (4.75-30)	10 (3-20)	30 (20-50)	<.001*
COVID-19 severity				**<.001**†
Mild	150 (14.75)	150 (15.34)	0 (0)	
Moderate	224 (22.03)	220 (22.49)	4 (10.26)	
Severe	310 (30.48)	297 (30.37)	13 (33.33)	
Critical	333 (32.74)	311 (31.8)	22 (56.41)	
Signs and symptoms				
Cough	543 (53.39)	515 (52.66)	28 (71.79)	**.019**†
Fever	520 (51.13)	503 (51.43)	17 (43.59)	.337†
Shortness of breath	105 (10.32)	103 (10.53)	2 (5.13)	.420‡
Dyspnea	335 (32.94)	314 (32.11)	21 (53.85)	.005†
Fatigue	67 (6.59)	65 (6.65)	2 (5.13)	.999‡
Anorexia	48 (4.72)	46 (4.7)	2 (5.13)	.706‡
Diarrhea	109 (10.72)	106 (10.84)	3 (7.69)	.791‡
Diagnosis				-
Physician assessment	39 (3.83)	-	39 (100)	
Laboratory findings	0 (0)	-	0 (0)	
Duration of COPD diagnosis				-
≤6 months	25 (2.46)	-	25 (64.10)	
>6 months	4 (0.39)	-	14 (35.90)	
GOLD Classification				-
GOLD A	12 (1.18)	-	12 (30.77)	
GOLD B	2 (0.20)	-	2 (5.13)	
GOLD C	14 (1.38)	-	14 (35.9)	
GOLD D	11 (1.08)	-	11 (28.21)	

*Statistical tests used: * – Mann-Whiney U test; † – Chi-square test; ‡ – Fisher's exact test.*

Table 2. Management and Outcomes of Patients, by COPD Status

	All (n=1017)	No COPD (n=978)	With COPD (n=39)	*P*
	Frequency (%); Median (IQR)			
COVID-19 management				
Oxygen therapy	583 (57.33)	552 (56.44)	31 (79.49)	**.004**†
HFNC	219 (21.53)	202 (20.65)	17 (43.59)	**.001**†
Mechanical ventilation	207 (20.35)	194 (19.84)	13 (33.33)	**.040**†
Remdesivir	162 (15.93)	153 (15.64)	9 (23.08)	.214†
Tocilizumab	194 (19.08)	181 (18.51)	13 (33.33)	**.021**†
Convalescent plasma therapy	69 (6.78)	62 (6.34)	7 (17.95)	**.013**‡
Hemoperfusion	63 (6.19)	62 (6.34)	1 (2.56)	.507‡
Dexamethasone	545 (53.59)	513 (52.45)	32 (82.05)	**<.001**†
Hospital days	12 (7-17)	12 (7-17)	14 (9-22)	**.024***
Mild COVID [n=150]	10 (5-12)	10 (5-12)	-	-
Moderate COVID [n=224]	10 (7-14)	10 (7-14)	10 (8.5-13)	.867*
Severe COVID [n=310]	16 (11-22)	13 (9-18)	16 (11-22)	.408*
Critical COVID [n=333]	13 (6-20)	13 (6-20)	15.5 (10-22)	.174*
Readmission	7 (0.69)	7 (0.72)	0 (0)	.999‡
Mortality	218 (21.44)	206 (21.06)	12 (30.77)	.148†
Mild COVID-19 [n=150]	2 (1.33)	2 (1.33)	-	.999‡
Moderate COVID-19 [n=224]	4 (1.79)	4 (1.82)	0 (0)	.999‡
Severe COVID-19 [n=310]	17 (5.48)	17 (5.72)	0 (0)	.693†
Critical COVID-19 [n=333]	195 (58.56)	183 (58.84)	12 (54.55)	

*Statistical tests used: * – Mann-Whiney U test; † – Chi-square test; ‡ – Fisher's exact test.*

Table 3. Mortality among Patients, by COPD Status and Severity

	N	Fatality	Proportion (95% CI)
No COPD	978	206	21.06 (18.55–23.76)
With COPD	39	12	30.77 (17.02–47.57)
GOLD A	12	1	8.33 (0.21–38.48)
GOLD B	2	1	50 (1.26–98.74)
GOLD C	14	4	28.57 (8.39–58.10)
GOLD D	11	6	54.55 (23.38–83.25)

Table 4 shows a univariate analysis for risk factors of mortality. Age, presence of hypertension, diabetes mellitus, malignancy, history of tuberculosis, positive smoking history, and use on investigational therapies for COVID-19 such as Remdesivir, Tocilizumab, Dexamethasone or combination of all were significantly associated with mortality. There was no sufficient evidence to support that COPD is a significant predictor of in-hospital mortality.

Logistic models are presented in Table 5, one with full predictors and another with only significant factors retained. In the former model, COPD status was not predictive of outcome of mortality (P = .267). In the latter, predicted odds of mortality inflated nearly five-fold (95% CI 2.79-7.93) in the presence of malignancy; six-fold (95% CI 3.94-9.14) if with management by remdesivir, tocilizumab, dexamethasone, or CPT; by 63.9% (95% CI 16%-132%) if with smoking history; and by 1.1% (95% CI 0.06%-2%) for every additional year of patient age. As with previous studies, presence of comorbidities conferred a higher risk for severe outcomes and mortality for the patient with COVID-19.[1-2,4-6,10,17-20] Smoking as a risk factor for severe disease and mortality in patients with COVID-19 infection has been described in previous literature.[5-6,10] In a systematic review and meta-analysis by Alqahtani, it was found that 22.3% of current smokers and 46% of ex-smokers had severe complications and mortality rate up to 38.5% in current smokers. Current smokers with 1.45 times more likely to have severe disease compared to former and never smokers.[6] In a meta-analysis by Shi et al., current smokers with COVID-19 infection were 2.95 times more likely to die than non-smokers.[19]

DISCUSSION

The prevalence of COPD in the study is comparable to the prevalence of COPD in other studies as previously stated. Majority of the patients were diagnosed within the last six months mostly because COPD may be under recognized and underdiagnosed in the community especially in a developing country like the Philippines leading to its diagnosis only when the patient seeks consult in the hospital for another reason such as in this case for COVID-19 infection.

COVID patients with COPD were older, male, smokers, with history of hypertension. They more commonly required oxygen support, HFNC, mechanical ventilation, Tocilizumab, Convalescent plasma therapy, and Dexamethasone, and had a longer median length of hospital stay at 14 days. This may be due to the fact that COPD patients have moderate to severe COVID thus needing more intensive treatment as compared to those without COPD.

Mortality rates for patient with COPD and without COPD from this study was consistent to other studies done.

Table 4. Univariate Analysis for Risk Factors of Mortality

	Died (n=218)	Survived (n=799)	Crude OR (95% CI)	*p*
COPD	12 (5.5)	27 (3.38)	1.666 (0.83-3.34)	.151
Age, years	60 (47-69)	53 (38-64)	1.024 (1.02-1.03)	**<.001**
Male	121 (55.5)	401 (50.19)	1.238 (0.92-1.67)	.164
Any comorbidity	176 (80.73)	549 (68.71)	1.908 (1.32-2.76)	**.001**
Hypertension	120 (55.05)	380 (47.56)	1.350 (0.99-1.82)	**.050**
Diabetes mellitus	68 (31.19)	215 (26.91)	1.231 (0.89-1.71)	.211
Cardiovascular disease	21 (9.63)	83 (10.39)	0.920 (0.56-1.52)	.744
Chronic kidney disease	21 (9.63)	60 (7.51)	1.313 (0.78 (2.21)	.306
Chronic liver disease	5 (2.29)	6 (0.75)	3.103 (0.94-10.26)	.064
Malignancy	39 (17.89)	41 (5.13)	4.028 (2.52-6.43)	**<.001**
Asthma	19 (8.72)	76 (9.51)	0.908 (0.54-1.54)	.720
History of TB disease	38 (17.43)	90 (11.26)	1.663 (1.10-2.51)	**.016**
Smoking history	79 (36.24)	197 (24.66)	1.737 (1.26-2.39)	**.001**
COVID-19 management				
Remdesivir	50 (22.94)	112 (14.02)	1.826 (1.26-2.65)	**.002**
Tocilizumab	77 (35.32)	117 (14.64)	3.183 (2.27-4.47)	**<.001**
Convalescent plasma therapy	16 (7.34)	53 (6.63)	1.115 (0.62-1.99)	.713
Dexamethasone	182 (83.49)	363 (45.43)	6.072 (4.14-8.91)	**<.001**
Remdesivir/CPT/Dexamethasone/TCZ	186 (85.32)	381 (47.68)	6.378 (4.27-9.51)	**<.001**

Table 5. Multivariate Analysis for Risk Factors of Mortality

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
COPD	0.635 (0.28-1.42)	.267	-	-
Age, years	1.014 (1.002-1.03)	**.023**	1.011 (1.0006-1.02)	**.039**
Male	1.053 (0.73-1.51)	.780	-	-
Any comorbidity				
Hypertension	0.881 (0.6-1.29)	.516	-	-
Diabetes mellitus	1.039 (0.71-1.52)	.845	-	-
Cardiovascular disease	0.675 (0.39-1.18)	.170	-	-
Chronic kidney disease	1.176 (0.64-2.15)	.597	-	-
Chronic liver disease	1.75 (0.44-6.98)	.428	-	-
Malignancy	4.421 (2.58-7.59)	**<.001**	4.702 (2.79-7.93)	**<.001**
Asthma	0.949 (0.53-1.7)	.861	-	-
Past or present TB disease	1.398 (0.87-2.24)	.163	-	-
Smoking history	1.692 (1.14-2.52)	**.010**	1.639 (1.16-2.32)	**.005**
Remdesivir/CPT/Dexamethasone/TCZ	6.153 (4.02-9.41)	**<.001**	5.997 (3.94-9.14)	**<.001**
Pseudo-R²	15.28%, *P* <.001		14.67%, *P* <.001	

Model 1: All variables were included in the multivariable logistic regression.
Model 2: Backward logistic regression was employed.

Upon analysis of mortality in GOLD grades, those under GOLD B and GOLD D were higher and this may be due to the fact that patients under GOLD B and GOLD D are more symptomatic probably due to poor symptom control from medications or more severe disease.[16] COPD was not a predictive outcome of mortality but smoking is a risk factor for severe disease.

This current study has several limitations. The time frame of admission of the patients included in the study spanned only six months. A longer time frame and subsequently a larger sample size would probably include more COPD patients and it would also show us the effect of the previous two surges of COVID-19 cases specifically from the Delta and Omicron variant on COPD. The diagnosis of COPD was based mostly on physician assessment and not on spirometry, and results from this study are not comparable to those derived from more objective definitions of COPD.

CONCLUSION

COPD patients are at increased risk for severe disease and longer length of hospital stay but the presence of COPD

as a comorbidity does not have a significant association with mortality. Significant predictors for mortality include older age, smoking, presence of malignancy, and use of investigational therapy (Remdesivir, Tocilizumab, CPT or Dexamethasone).

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

Both authors declared no conflicts of interest.

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