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Implication of chronic obstructive pulmonary disease on the severity and outcome of covid-19 in rural India; Is COPD the hidden culprit amongst the havoc: A cross sectional study

Dhruv Talwar[1], **Sunil Kumar**[2*], **Sourya Acharya**[2], **Deepak Talwar**[3], **Shraddha Jain**[4], **Neema Acharya**[5], **Kamlesh Chaudhari**[5], **Sparsh Madaan**[6], **Vidyashree Hulkoti**[1], **Akhilesh Annadatha**[1], **Twinkle Pawar**[1], **Mansi Patel**[1], **Divit Shah**[1]

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Authors' Affiliation:
[1]Post Graduate Resident, Department of Medicine, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi meghe, Wardha, Maharashtra, India
[2]Professor, Department of Medicine, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi meghe, Wardha, Maharashtra, India
[3]Chairman, Metro Centre for Respiratory Diseases, Noida, Uttar Pradesh, India
[4]Professor, Department of Otolaryngology, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi meghe, Wardha, Maharashtra, India
[5]Professor, Department of obstetrics and gynaecology, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi meghe, Wardha, Maharashtra, India
[6]Post Graduate Resident, Department of obstetrics and gynaecology, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi meghe, Wardha, Maharashtra, India

[*]**Corresponding author**
Professor, Department of Medicine, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences
(Deemed to be University), Sawangi meghe, Wardha, Maharashtra, India
Email: sunilkumarmed@gmail.com

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ABSTRACT

COVID-19 (Coronavirus infectious disease 2019) denotes an ever changing and varied disease which has crippled the health care systems throughout the world. There have been studies conducted across the globe to establish the important factors for severity and mortality associated with COVID-19. We tried to study the effect of chronic obstructive pulmonary disease (COPD) on the severity as well as outcome of COVID-19. *Material and methods*: A total of 180 patients with COVID-19 were enrolled in this study and were then screened for history of COPD. There were 49 patients with history of COPD and 131 patients with no history of COPD. Inflammatory markers and HRCT scores were assessed for all the patients and they were followed up to study the outcome. *Result:* COPD was significantly associated HRCT Score, inflammatory markers and outcome. The mean HRCT Score for patients with COPD was more in COPD group (15.39 ± 4.65) when compared with Non-COPD group (9.39 ± 3.98). Mortality was also significantly higher in patients with COPD (67.3%) when compared to the patients without COPD (3.3%). *Conclusion:* We conclude that COPD is an important factor which has to be considered while treating the patients of COVID-19 especially in the rural India where lockdown restrictions and lack of knowledge have provided hinderance in achieving optimal follow up as there is increased severity and mortality associated with it.

Keywords: Chronic obstructive pulmonary disease, COVID-19, Severtiy, Outcome, Mortality

1. INTRODUCTION

Coronavirus disease 2019 that results from the infection by sever acute respiratory syndrome coronavirus 2 (SARS CoV2) has resulted in the formation of a lethal pandemic affecting mortality and morbidity throughout the world (Atzrodt et al., 2020). The disease severity might vary from benign infection of the respiratory system to severe pneumonia, acute respiratory distress syndrome (ARDS) as well as death. There is lack of proper knowledge as well a relatively new viral infection has crippled the health care facilities with difficulties in predicting outcomes and high risk individuals while admitting a patients with COVID-19. Patients who suffer from chronic respiratory disease specially COPD have a relatively higher risk of contracting COVID-19 which can be explained by their poor underlying lung reserve and small airways having overexpression of angiotensin-converting enzyme 2 (ACE-2) receptors (Leung et al., 2020). There is however, a paucity of data available on COPD and its effect on the clinical course and outcome in COVID-19 patients.

Guan et al., (2020) studied the patients of COVID-19 in China for serious adverse outcomes after stratification of patients by the co-morbidities. It was concluded in this study that the highest hazard ratio of 2.68 was found for COPD patients. However, while battling the pandemic of COVID-19 worldwide, COPD could not be focussed upon due to the uncertainty of the disease, varied presentations and as the healthcare workers were busy managing the pandemic.

2. MATERIAL AND METHODS

A total 180 patients with positive reverse transcriptase for polymerase chain reaction (RT-PCR) were enrolled for the study who was admitted in the Intensive Care Unit since May 2021 to July 2021. Inclusion criteria was patients who were diagnosed with COVID-19 through the means of RT-PCR for SARS Cov-2,aged 18 years or more and provided admission in the intensive care unit (ICU). Exclusion criteria were pregnant patients and the patients who declined to provide informed consent for the study.

A total of 374 patients admitted to the COVID Intensive Care Unit between the periods of April to July were considered for this study. After the utility of the exclusion criteria a total of 180 patients who met the inclusion criteria were finally included as participants in the study after acquiring proper informed consent. A 25-Point Computed Tomography Severity Score was used to assess the HRCT which carried out within 24 hours of admission which is a globally used scale for assessing severity of lung parenchymal involvement in COVID-19. All the enrolled patients were screened for history of COPD and about any known previous illness.

All the patients were screened for various diseases including COPD through a baseline chest radiograph, IHD (ischemic heart disease) through a baseline electrocardiography, hypertension through recorded blood pressure, diabetes mellitus on the basis of fasting and post prandial blood sugar levels and glycosylated haemoglobin levels all recorded within one day (twenty four hours) of admitting the patients. All the patients were observed for the outcome in terms of cure or death.

Laboratory measurements

Reverse Transcriptase -Polymerase chain Reaction for Severe Acute Respiratory Syndrome-Coronavirus-2 was used in diagnosing COVID-19 in the nasopharyngeal swab. The central clinical laboratory based in Jawaharlal Nehru Medical College, Sawangi meghe, Wardha was responsible for diagnosing COVID-19 for the 180 patients who were enrolled for this study. This laboratory has been authorised by the Indian Council of Medical Research in order to conduct RT-PCR for diagnosing COVID-19. RT-PCR Quant Studio 5 was used for conducting reverse transcriptase polymerase chain reaction which works on the principle of reverse transcription of the ribonucleic acid to obtain deoxyribonucleic acid for the purpose of amplification. Meril COVID-19 One-Step RT-PCR kit was the kit which was used for RT-PCR containing the enzyme mix for COVID-19 which was lyophilized, mix buffer, Primer-probe mix for COVID-19, enzyme mix buffer, control for COVID-19 Polymerase Chain Reaction positive as well as negative.

Levels of interleukin 6 were assayed by the method of ELISA (enzyme-linked immunosorbent assay). Interleukin 6 determination was done through the human enzyme-linked immunosorbent assay kit for Interleukin 6 having sensitivity of less than 1pg/ml. Normal levels of interleukin 6 were considered to be 1 to 7pg/ml and a value obtained above the level of 7pg/ml was marked to be raised.

Integrated VITROS 5600 system working through the electrochemiluminescence immunoassay principle was used to determine level of serum ferritin. Ferritin reagent which was ready to be used, Elecsys Ferritin and CalSe comprised the kit which was used for ferritin level assay. Normal range for ferritin levels was considered starting from twenty four to three hundred and thirty six micrograms per liter. Values which were raised were defined as more than three hundred and thirty six micrograms per liter. The method of Lactate kinetic was performed for measuring the value of Serum lactate dehydrogenase with normal values ranging from 140 to 280 U/L. Any value measured above 280 Units per liter was declared to be raised.

Immunoturbidimetry was utilised in order to obtain Serum C-reactive protein levels with a normal range considered from 8-10 mg/L. Any measured value above the level 10mg/l was declared as raised. Automated latex enhanced immunoassay was used to measure D-Dimer level with a normal range below or equal to 500 ng/ml fibrinogen-equivalent units. Any measured value greater than five hundred nano gram per ml fibrinogen-equivalent units was declared as raised.

Statistical analysis

Data was analysed and expressed through the measures of percentages (%), mean along with Standard Deviation, or median and twenty five to seventy five percent inter-quartile range (IQR), as appropriate. All the enrolled subjects were classified as COPD group and non COPD group and were further divided into discharged and death group based on outcome. Variables which were dichotomus were drafted using clinically relevant thresholds. Variables that were continuous as well as distributed normally were compared using t-test however Mann-Whitney U-test was performed for non-normally distributed variables. Analysis was done by thee SPSS software version 21. All the statistical analysis was performed were two tailed. Value of less than 0.05 for p-value was declared to be significant statistically.

3. RESULTS

HRCT Score, IL-6 (pg/mL), TLC (/mm^3), Heart Rate >120, Respiratory Rate > 20, Systolic BP <90, D-Dimer (ng/mL), Ferritin (ng/mL), LDH (U/L), ESR (mm/Hr), CRP (mg/L) and Outcome were significantly associated ($p<0.05$) with COPD as shown in table 1.

Table 1 Association between COPD and Parameters

Parameters	COPD		p value
	Yes (n = 49)	No (n = 131)	
Age (Years)	59.78 ± 16.39	56.65 ± 14.30	0.247[1]
Age Group			0.427[2]
18-40 Years	6 (12.2%)	18 (14.0%)	
40-60 Years	17 (34.7%)	58 (43.8%)	
>60 Years	26 (53.1%)	55 (42.1%)	
Gender***			0.026[2]
Male	38 (77.6%)	78 (59.5%)	
Female	11 (22.4%)	53 (40.5%)	
HRCT Score***	15.39 ± 4.65	9.39 ± 3.98	<0.001[3]
IL-6 (pg/mL)***	208.75 ± 175.57	110.77 ± 104.99	<0.001[3]
TLC (/mm^3)***	9802.24 ± 4814.00	7956.37 ± 3479.03	0.012[3]
Heart Rate >100 (Yes)***	34 (69.4%)	6 (5.0%)	<0.001[2]
Respiratory Rate > 20 (Yes)***	33 (67.3%)	3 (2.5%)	<0.001[2]
D-Dimer (ng/mL)***	3.59 ± 2.45	2.00 ± 5.25	<0.001[3]
Ferritin (ng/mL)***	939.75 ± 683.40	471.00 ± 417.99	<0.001[3]
LDH (U/L)***	834.45 ± 400.39	371.55 ± 303.90	<0.001[3]
ESR (mm/Hr)***	170.61 ± 144.04	64.50 ± 43.15	<0.001[3]
CRP (mg/L)***	34.76 ± 24.18	7.44 ± 12.47	<0.001[3]
Outcome***			<0.001[2]
Discharge	16 (32.7%)	127 (96.7%)	
Death	33 (67.3%)	4 (3.3%)	

****Significant at p<0.05, 1: t-test, 2: Chi-Squared Test, 3: Wilcoxon-Mann-Whitney U Test*

The mean (SD) of Age (Years) in the COPD group was 59.78 (16.39). While the mean (SD) of Age (Years) in the Non-COPD group was 56.65 (14.30). The median (IQR) of Age (Years) in the COPD group was 62 (49-70) whereas the median (IQR) of Age (Years) in the non COPD group was 57 (47-66). The Age (Years) in the COPD group ranged was from 25 - 89. The Age (Years) in the non COPD group was ranged from 24 - 85. The variable HRCT Score was not normally distributed in the 2 subgroups of the

variable COPD. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons shown in table 2.

Table 2 Comparison of the 2 Subgroups of the Variable COPD in Terms of HRCT Score (n = 180)

HRCT Score	COPD		Wilcoxon-Mann-Whitney U Test	
	Yes	No	W	p value
Mean (SD)	15.39 (4.65)	9.39 (3.98)	5007.000	<0.001
Median (IQR)	16 (14-18)	9 (7-12)		
Range	2 - 23	1 - 21		

The mean (SD) of HRCT Score in the COPD group was 15.39 (4.65). The mean (SD) of HRCT Score in the non-COPD group was 9.39 (3.98). The median (IQR) of HRCT Score in the COPD group was 16 (14-18). The median (IQR) of HRCT Score in the non-COPD group was 9 (7-12). The HRCT Score in the COPD group ranged from 2 - 23. The HRCT Score in the non-COPD group ranged from 1 - 21. The difference between the two groups in terms of HRCT Score was significant (W = 5007.000, p = <0.001), with the median HRCT Score being highest in the COPD group.

Strength of Association (Point-Biserial Correlation) = 0.55 (Large Effect Size)

The Box-and-Whisker plot below (figure 1) depicts the distribution of HRCT Score in the 2 groups. The middle horizontal line represents the median HRCT Score, the upper and lower bounds of the box represent the 75th and the 25th centile of HRCT Score respectively, and the upper and lower extent of the whiskers represent the Tukey limits for HRCT Score in each of the groups. Chi-squared test was used to explore the association between 'COPD' and 'Outcome' as shown in table 3.

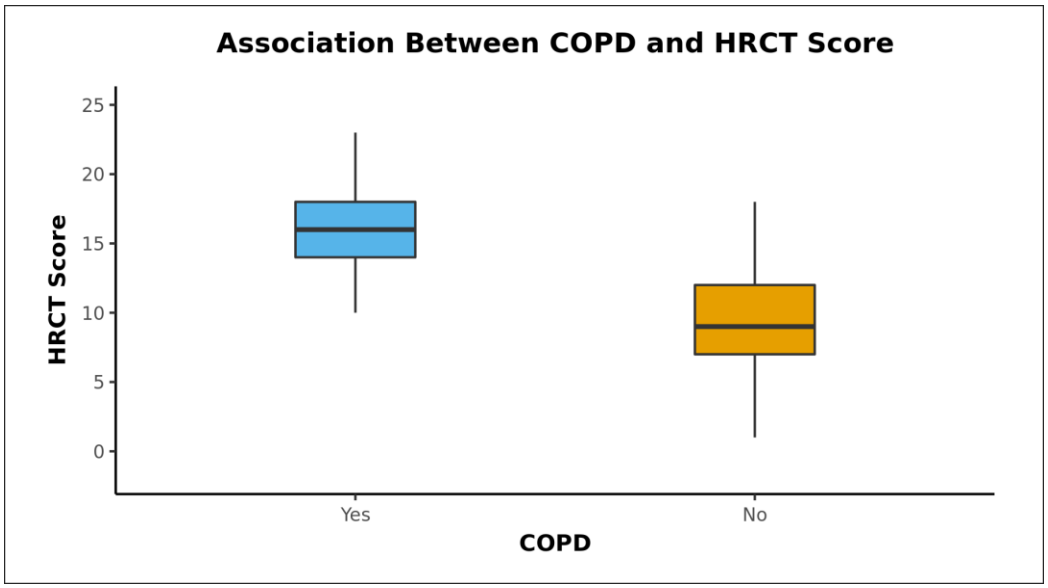

Figure 1 Box and whisker plot depicting distribution of HRCT Score amongst subjects

Table 3 Association between COPD and Outcome (n = 180)

Outcome	COPD			Chi-Squared Test	
	Yes	No	Total	$\chi 2$	P Value
Discharge	16 (32.7%)	127 (96.7%)	143 (79.4%)	84.003	<0.001
Death	33 (67.3%)	4 (3.3%)	37 (20.6%)		
Total	49 (100.0%)	131 (100.0%)	180 (100.0%)		

The difference found in the groups in terms of distribution of Outcome was significant ($\chi 2$ = 84.003, p = <0.001).
Strength of association between the two variables (Cramer's V) = 0.7 (High Association)
Strength of association between the two variables (Bias Corrected Cramer's V) = 0.7 (High Association)

32.7% of the participants in the group COPD group were discharged whereas 67.3% of the participants had expired. 96.7% of the participants in the group non COPD group were discharged whereas 3.3% of the participants expired. Participants in the non-COPD group had the larger proportion of Discharge as outcome whereas Participants in the COPD group had the larger proportion of death as outcome.

Regression analysis for HRCT Score

Regression with all variables in model

Table 4 summarizes the regression analysis for the dependent variable using all the predictor variables together in one go. The 'Coefficient (univariable)' column lists the regression coefficient for each of the variables with respect to the dependent variable, when these variables were used as single predictors of the dependent variable, without entering the rest of the variables in the model. The 'Coefficient (multivariable)' column lists the coefficients for all the variables when they were entered in the model together (and are now thus controlling for each other). The first category in each of the categorical variables is the reference category, against which the coefficients of the rest of the variables were calculated.

Table 4 Showing Regression with all variables in model

Dependent: HRCT Score		unit	value	Coefficient (univariable)	Coefficient (multivariable)
DM	No	Mean (sd)	9.2 (3.3)	-	-
	Yes	Mean (sd)	13.1 (5.6)	3.92 (2.53 to 5.31, p<0.001)	1.07 (-0.69 to 2.82, p=0.232)
HTN	No	Mean (sd)	9.2 (2.8)	-	-
	Yes	Mean (sd)	12.0 (5.5)	2.83 (1.25 to 4.41, p=0.001)	-0.12 (-2.03 to 1.79, p=0.899)
IHD	No	Mean (sd)	9.0 (3.0)	-	-
	Yes	Mean (sd)	12.9 (5.7)	3.89 (2.49 to 5.28, p<0.001)	1.43 (-0.84 to 3.69, p=0.216)
COPD	No	Mean (sd)	9.4 (4.0)	-	-
	Yes	Mean (sd)	15.4 (4.7)	6.00 (4.60 to 7.40, p<0.001)	5.15 (3.40 to 6.90, p<0.001)
Obesity	No	Mean (sd)	9.6 (3.2)	-	-
	Yes	Mean (sd)	12.3 (5.7)	2.77 (1.30 to 4.24, p<0.001)	-0.92 (-2.63 to 0.79, p=0.288)

MODEL FIT: F(5,164) = 15.9, p = <0.001

Number in data frame = 180, Number in model = 180, Missing = 0, Log-likelihood = -480.17

AIC = 974.3, R-squared = 0.33, Adjusted R-squared = 0.31

Regression with selected variables in model

Table 5 shows 'Bidirectional Stepwise Selection' select only the most useful variables to include in the final multivariable predictive model for the dependent variable.

Table 5 Showing Regression with selected variables in model

Dependent: HRCT Score		unit	value	Coefficient (univariable)	Coefficient (multivariable)
DM	No	Mean (sd)	9.2 (3.3)	-	-
	Yes	Mean (sd)	13.1 (5.6)	3.92 (2.53 to 5.31, p<0.001)	1.58 (0.13 to 3.04, p=0.033)
HTN	No	Mean (sd)	9.2 (2.8)	-	-
	Yes	Mean (sd)	12.0 (5.5)	2.83 (1.25 to 4.41, p=0.001)	-
IHD	No	Mean (sd)	9.0 (3.0)	-	-
	Yes	Mean (sd)	12.9 (5.7)	3.89 (2.49 to 5.28, p<0.001)	-
COPD	No	Mean (sd)	9.4 (4.0)	-	-

Dependent: HRCT Score		unit	value	Coefficient (univariable)	Coefficient (multivariable)
Obesity	Yes	Mean (sd)	15.4 (4.7)	6.00 (4.60 to 7.40, p<0.001)	5.12 (3.52 to 6.72, p<0.001)
	No	Mean (sd)	9.6 (3.2)	-	-
	Yes	Mean (sd)	12.3 (5.7)	2.77 (1.30 to 4.24, p<0.001)	-
MODEL FIT: F(2,167) = 38.93, p = <0.001					
Number in data frame = 180, Number in model = 180, Missing = 0, Log-likelihood = -481.24					
AIC = 970.5, R-squared = 0.32, Adjusted R-squared = 0.31					

4. DISCUSSION

COPD is a lung disease encountered commonly which is linked to a limitation in the airflow (Talwar et al., 2021). The predominant culprit behind this disease remains exposure to noxious gas as well as particulate matter for long duration resulting in abnormalities of the alveoli and the airway (Lopex-Campos et al., 2016). Acute deterioration in patients of COPD may result from various factors with viral infection being an important trigger. The expression of angiotensin convertase enzyme 2 receptor genes increased significantly in COPD (Leung et al., 2020). Angiotensin convertase enzyme 2 is the receptor modulated by SARS CoV 2. There was also an inverse relationship seen between expression of angiotensin convertase enzyme 2 genes and FEV1 percentage (Yin et al., 2020). The status of smoking was also highly associated with expression of angiotensin convertase enzyme 2 gene receptor levels in the patient's airways with patients (Yin et al., 2020).

Current smokers also had significantly raised expression of gene for angiotensin convertase enzyme 2 receptor when compared to non-smokers. Studies state that even after adjustment for status of smoking, the association of angiotensin convertase enzyme 2 with COPD was still significant (Purohit et al., 2021). Also, in the systematic review conducted by Purohit et al., (2021) stated that out of all the chronic lung disorders the highest increase in the genes for angiotensin convertase enzyme 2 was associated with COPD when compared to lung tissue obtained from healthy lung. In our study mortality was 67.3 percent in patients of COPD when compared to non-COPD group (3.3%). This drastic increase in mortality may be associated with this increase of angiotensin convertase enzyme 2 receptor expression in chronic obstructive pulmonary disease patients.

Higham et al., (2020) stated in a study that lung tissue of obese COPD patients had increased amount of angiotensin convertase enzyme 2 receptor explains the finding of our study with COPD and obesity the two co-morbidities with most significant impact on outcome. In an metanalysis conducted by Alqahatani et al., (2020) it was stated that COPD affected COVID-19 by increasing severity by 63 percent and mortality by 60 percent. Inflammatory markers such as interleukin 6, d-dimer, ferritin, lactate dehydrogenase and C - reactive protein were also found to be raised significantly in the subjects with COPD in our study further strengthening the association of COPD with severity of COVID-19. However cardiovascular comorbidities was reported to be more significantly affecting mortality and severity when compared to COPD in the above study conducted by Alqahatani et al., (2020) which was different from inference of our study.

In an observational study Gupta et al., (2021) found significant reduction in the hospitalisation due to COPD in the COVID-19 era owing to the practice of wearing masks and lockdown. Also, in a metanalysis conducted by Singh et al., (2020) the total combined prevalence of COPD in COVID-19 patients was four percent. This was contrary to the findings of our study where we found that a substantial 27.2 % of the subjects who were provided admission due to COVID-19 in ICU and enrolled in our study had chronic obstructive pulmonary disease. In a systematic review conducted by Aggarwal et al., (2021) it was found that COPD patients with COVID-19 had higher ICU admissions, need of intubation and morality which was similar to the results of our study.

Our research was performed in a rural centre of central India. With the emergence of COVID-19 and the lockdown restrictions imposed for prevention of SARS CoV-2 transmission, there is difficulty amongst the rural population in reaching healthcare centres (Kumar et al., 2020). The above reason can be the probable culprit for COPD patients being unable to reach health care professionals for proper follow up further increasing the morbidity and mortality amongst COPD due to COVID-19. This emphasis on the fact that there has to be proper follow up of patients with chronic diseases of lung in the ongoing pandemic as that is the at risk population of developing severe COVID-19 infection as well as adverse outcomes. The inflammatory markers HRCT score and respiratory rate which were significantly raised were measured on admission thus signifying that such patients approached to the healthcare centres only when the disease had progressed and not in the initial phase of the disease. Patients having COPD residing in the rural parts of India should therefore be educated and made aware of the symptoms and signs of COVID-19 in order to aid them in deciding when to seek healthcare help.

Although research has been conducted in rural central India regarding various parameters of COVID-19 including role of zinc (Kumar et al., 2022), haematological manifestations (Baviskar et al., 2021), endocrine manifestations (Jaiswal et al., 2021) and role of inflammatory markers (Talwar et al., 2022) as well as novel scoring systems (Kumar et al., 2021), there is paucity of data regarding probable influence of COVID-19 seen in subjects with COPD in this area making this an important study in order to raise awareness.

Limitations

Limitations of the present research include the relatively smaller sample size as this research was performed in a single center when compared to other studies based on COVID-19. As the number of patients who were enrolled were less, findings of Odds ratio for Ischemic heart disease, diabetes mellitus and hypertension for logistic regression were calculated to be infinity due to the chance finding of having no mortality in patients without these co-morbidities in a rather small sample size hence we excluded this analysis from the study. Also, as this study was based in central India at a hospital with limited resources, serial inflammatory markers and repeat HRCT could not be done for the enrolled patients to look for the progression of the disease. Another limitation is as the patients were positive for COVID-19; pulmonary function test was not done.

5. CONCLUSION

COPD is an important co-morbidity which significantly affects not only the severity but also the outcome in COVID-19. Patients suffering from COPD should therefore be provided special attention by the clinicians while treating COVID-19 as there is increased probability of adverse outcome in such patients. Awareness and education of COPD patients should be done specially in the rural parts of India in order to prevent COVID-19 infection and to ensure that they do not delay presenting to health care centres whenever required.

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Author Contributions

All authors have contributed to the design of the study, as well as data collection and analysis, and the writing of the manuscript. All authors have read and approved the final manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of Datta Meghe Insittute of Medical Sciences and Research with ethical approval code: DMIMS (DU)/IEC/2020-21/89.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES AND NOTES

1. Aggarwal A, Agarwal R, Dhooria S, Prasad K, Sehgal I, Muthu V. Impact of chronic obstructive pulmonary disease on severity and outcomes in COVID-19 patients: A systematic review. Int J Noncommun Dis 2021; 6:10. https://doi.org/10.4103/jncd.jncd_7_21.
2. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, Quaderi S, Mandal S, Hurst JR. Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis. PLoS One 2020; 15(5):e0233147. doi: 10.1371/journal.pone.0233147.

3. Atzrodt CL, Maknojia I, McCarthy RDP. A Guide to COVID-19: a global pandemic caused by the novel coronavirus SARS-CoV-2. FEBS J 2020; 287(17):3633-3650. doi:10.1111/febs.15375
4. Bawiskar N, Talwar D, Acharya S, Kumar S. Hematological Manifestations of COVID-19 and Their Prognostic Significance in an Intensive Care Unit: A Cross-Sectional Study. Cureus 2021; 13(11):e19887. doi: 10.7759/cureus.19887.
5. Guan WJ, Liang WH, Zhao Y. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55(5):2000547.doi:10.1183/13993003.00547-2020
6. Gupta N, Dhar R, Swarnakar R, Bedi R, Chawla R. Impact of COVID-19 on (Non-COVID) chronic respiratory disease outcome survey in India (CCROS study). Lung India 2021; 38:454–9. doi:.4103/lungindia.lungindia_965_20.
7. Higham A, Singh D. Increased ACE2 Expression in Bronchial Epithelium of COPD Patients who are Overweight. Obesity (Silver Spring) 2020; 28(9):1586-1589. doi: 10.1002/oby.22907.
8. Jaiswal P, Kumar S, Acharya S, Bawankule S, Talwar D, Dhande R, BaggaC, Jugtap G, Verma P, Patel M, Khan S. Impact of covid 19 manifestationon thyroid function status in previously euthyroid patients: A crosssectional study. Medical Science 2021; 25(114): 1821-1826.
9. Kumar A, Rajasekharan Nayar K, Koya SF. COVID-19: Challenges and its consequences for rural health care in India. Public Health Pract (Oxf) 2020; 1:100009. doi:10.1016/j.puhip.2020.100009
10. Kumar S, Acharya S, Jain S. Role of Zinc and Clinicopathological Factors for COVID-19-Associated Mucormycosis (CAM) in a Rural Hospital of Central India: A Case-Control Study. Cureus 2022; 14(2): e22528. doi:10.7759/cureus.22528
11. Kumar S, Dronamraju S, Acharya S, Jaiswal P, Hulkoti V, Talwar D, Hepat S, Vs I, Shah D, Bhagawati J. COVID-PIRO (Predisposition, Insult, Response, Organ Dysfunction) Score: A Reliable Predictor of Outcomes in COVID-19 Patients Admitted in Intensive Care Unit. Cureus 2021; 13(10):e18960. doi: 10.7759/cureus.18960
12. Leung JM, Niikura M, Yang CWT, Sin DD. COVID-19 and COPD. Eur Respir J 2020; 56(2):2002108. doi:10.1183/13993003.02108-2020
13. Leung JM, Yang CX, Tam A. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J 2020; 55(5):2000688.doi:10.1183/13993003.00688-2020
14. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirol 2016; 21(1):14-23. doi:10.1111/resp.12660
15. Purohit D, Ahirwar AK, Sakarde A, Asia P, Gopal N. COVID-19 and lung pathologies. Horm Mol Biol Clin Investig 2021; 42(4):435-443. doi: 10.1515/hmbci-2020-0096. PMID: 34333882.
16. Singh AK, Gillies CL, Singh R, Singh A, Chudasama Y, Coles B, Seidu S, Zaccardi F, Davies MJ, Khunti K. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. Diabetes Obes Metab 2020; 22(10):1915-1924. doi: 10.1111/dom.14124.
17. Talwar D, Kumar S, Acharya S, Raisinghani N, Madaan S, Hulkoti V, Akhilesh A, Khanna S, Shah D, Nimkar S. Interleukin 6 and Its Correlation with COVID-19 in Terms of Outcomes in an Intensive Care Unit of a Rural Hospital: A Cross-sectional Study. Indian J Crit Care Med 2022; 26(1):39-42. doi: 10.5005/jp-journals-10071-24075.
18. Talwar D. Pulmonary rehabilitation, Lung India 2021; 38(3): 209-210. doi: 10.4103/lungindia.lungindia_7_21
19. Yin J, Kasper B, Petersen F, Yu X. Association of cigarette smoking, COPD, and lung cancer with expression of SARS-CoV-2 entry genes in human airway epithelial cells. Front Med (Lausanne) 2020; 7:619453.doi:10.3389/fmed.2020.61945