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THE STUDY ON COMORBIDITIES ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND THEIR IMPACT ON COPD PROGRESSION

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ABSTRACT
Background& aims: Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitations associated with systemic inflammation. There is strong associative evidence that the inflammatory cells/mediators in COPD are also relevant to the development of comorbidities. We aimed to study the comorbidities associated with COPD and their impact on COPD progression and also to assess markers in the blood to evaluate systemic inflammation and organ involvement
Methods: In this observational explorative clinical study, 108 patients with COPD diagnosed based on GOLD COPD criteria after spirometry were selected by systematic random sampling &evaluated for the presence of co-morbidities. Systemic inflammatory markers ESR, CRP& neutrophils, were evaluated. The results were tabulated in percentages and frequencies.
Results: Among the 108 patients with COPD, of which 99 were males & 9 were females with the majority belonging to 51-70 years (65%), the most common co-morbidities were Hypertension 36, GERD 26, RVF 20, Malnutrition 18, ischemic heart disease 13, Diabetes Mellitus 13, Depression 12. The patients with an increased number of comorbidities were associated with a progressive increase in the severity of obstruction and an increased number of hospital exacerbations. Patients with COPD who had a history of HTN, DM, dyslipidemia IHD, RVF, anemia, malnutrition, depression and GERD had increased CAT scores after 1 year of follow-up as compared to baseline value using a paired t-test with a p value of < 0.05.
Conclusion: COPD is frequently associated with various co-morbidities with consistent evidence that these co-morbidities have a great negative impact on COPD patients in terms of exacerbation, worsening airflow obstruction, health status and severity of dyspnea. Hence early detection and treatment of these comorbidities in COPD patients can prevent the development of complications in them due to the combined effect of both diseases.
Keywords: Chronic Obstructive Pulmonary Disease, Co-morbidities, Systemic Inflammation, Acute Exacerbation, quality of life.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms due to abnormalities of the airway and alveoli

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that causes persistent progressive airflow obstruction. It results from the gene-environmental interaction and these environmental exposures are tobacco smoking and inhalation of toxic particles and gases from household and outdoor air pollution[1].

COPD has a systemic effect due to spilling over of pulmonary inflammatory response into systemic circulation and activation of inflammatory cells during their transit through inflamed milieu in the lungs. CRP is an acute-phase protein, increased in the plasma of COPD patients during acute infective exacerbations. In stable COPD, plasma concentrations are related to mortality in mild to moderate patients· CRP binds to damaged tissue and leads to activation of the complement, resulting in endothelial injury and tissue inflammation. Chemotactic and proteolytic activity of circulating neutrophils are increased in patients with emphysema compared with normal smokers and nonsmokers, indicating an abnormality in circulating cells[2]

Globally, 3.17 million deaths were caused by COPD in 2015[3]. In India, median COPD prevalence is 5% in males and 2.7% in females in adults of 40 years of age and above.[4] It causes 8.7% of the total deaths and 4.8% of Disability Adjusted Life Years (DALY) in the country.

Comorbidities are a common cause of many COPD hospitalizations. In the Lung Health Study, 12.8% of the 5,887 smokers were hospitalized, with 42% of the hospitalizations secondary to cardiovascular events[5.] The systemic inflammation present in COPD induces a ‘‘pro-coagulant’’ state that leads to abnormally elevated levels of circulating thrombin–antithrombin complex and prothrombin activation fragments, with a parallel elevation in interleukin (IL)-6[6].

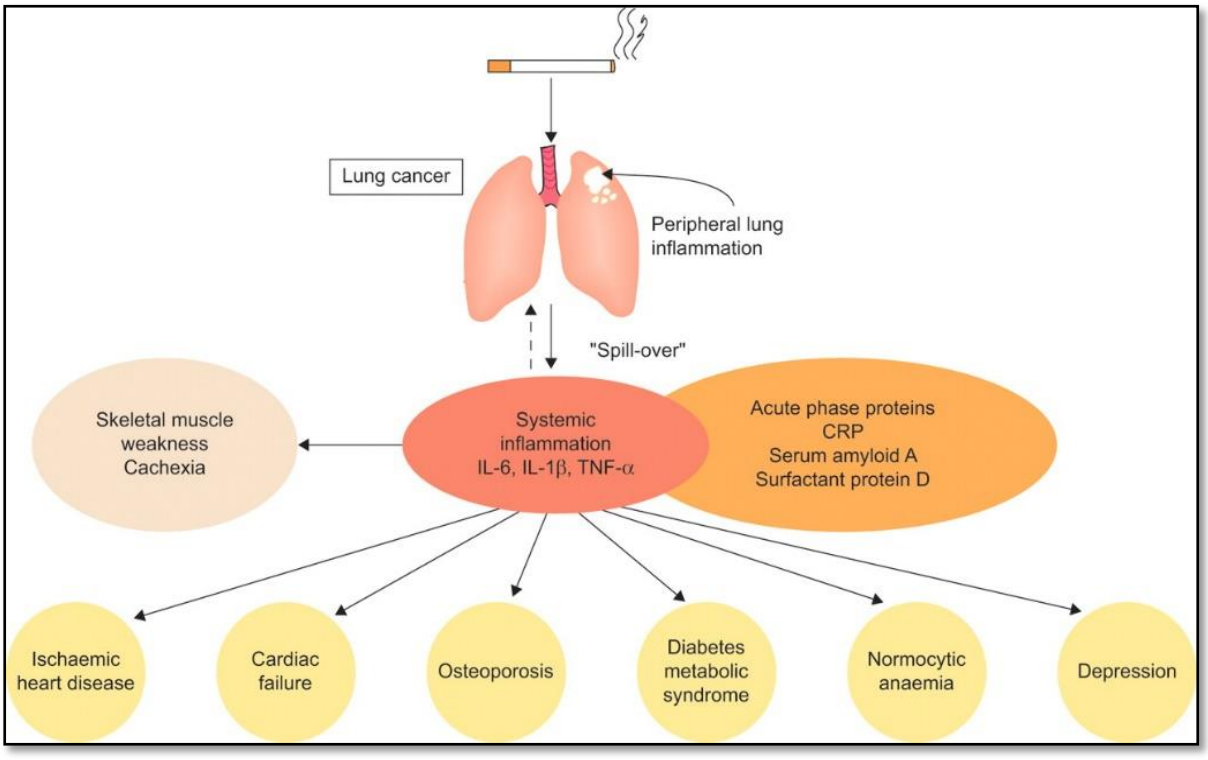

Figure 1: Systemic effects & Co-morbidities of Chronic Obstructive Pulmonary Disease

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The prevalence of PH in COPD is 5–40% [7]. Pulmonary artery remodelling in COPD leads to pulmonary hypertension (PH) which is the consequence of endothelial dysfunction and coagulopathy, hypoxic vasoconstriction, destruction of the pulmonary capillary bed by emphysema, smoking-induced inflammatory infiltration of the vascular wall [7]. The presence of PH in COPD worsens gas exchange and dyspnea, and predisposes to right ventricular dysfunction and peripheral edema. It is also associated with higher mortality.
A study, published in 2006 showed that exacerbation was high in patients with combined heart failure than stable COPD[8]. The b-blockers improve the survival of patients with heart failure, yet are commonly underused in patients with COPD, due to concerns that they will worsen the airway obstruction. Patients are therefore denied the full benefit of heart failure treatments. Switching to a cardio selective b-blocker improves spirometry values, without affecting the left ventricular ejection fraction enabling a better cardiac prognosis without the risk of compromising respiratory function.

Diabetes affects the prognosis of COPD (time to first hospitalization and 5-year mortality rate) [9.] Systemic inflammation plays an important role in both the progression of COPD and the development of insulin resistance.
The pulmonary consequences of diabetes and metabolic syndrome lead to a restrictive pattern due to reduced pulmonary elasticity through non-enzymatic glycosylation of tissue proteins, loss of inspiratory muscle strength and/or diaphragmatic compromise due to diabetic neuropathy. Elevations of IL-1, IL-6 and TNF-a, which have a harmful effect on erythropoiesis lead to anemia in COPD[10]. It interferes with their treatments, because respiratory rehabilitation is compromised by the patients.

Malnutrition in COPD is the consequence of inadequate intake caused by dyspnea resulting from the effort of eating and increased energy consumption including work of breathing. Patients with malnutrition has to be adviced to have caloric, protein and polyunsaturated fatty acid supplementation[11] should be integrated into a standardized programme. J ORDAN et al[12] reported a significant increase in deaths due to respiratory disease in subjects with a BMI of 40kg/m^2 (HR 5.78, 95% CI 1.09–30.61). Obese patients, especially those with COPD, should be investigated for obstructive sleep apnea syndrome (OSAS) and obesity hypoventilation syndrome

COPD patients with ischemic changes on their ECG have a significant decrease in their 6-minute walk distance, which correlates with increased mortality. Markers of cardiac dysfunction, such as troponin and BNP, have been shown to predict 30-day mortality following COPD exacerbations. Simple measures such as ECG, troponin, and BNP have been shown to be useful predictors of mortality and can inform physicians of the potentially reversible risk of IHD.

Depression predicts decreased quality of life, increased hospitalizations with longer lengths of stay, and increased mortality, further worsened by decreased likelihood of smoking cessation and poor adherence to medications and pulmonary rehabilitation. Standard therapies like cognitive behavioral therapy, antidepressants, and anxiolytics, reduce dyspnea, fatigue, and depression, and increase the quality of life. As hypoxia promotes erythropoiesis, Polycythemia contributes to the development of pulmonary hypertension, stroke, hypertension, vascular access thrombosis, cardiovascular events, end-stage renal disease and

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death.

As the severity of COPD increases, the prevalence of peptic ulcer disease and Helicobacter pylori also increased. Helicobacter may precipitate inflammation of the lung and thus increase response to inhaled stimuli such as smoking[13].

2. METHODS

Study design: Single group observational explorative clinical study

Study Technique: Systematic random sampling

Sample Size: Based on outcome variables on systemic inflammation and organ involvement with 86% prevalence among moderate to severe COPD patients derived from previous literature,99% confidence interval and 10% margin of error, the sample size of 108 was taken for the study

Study group: 108 patients who were diagnosed have COPD based on GOLD COPD criteria, who attended the outpatient department of Respiratory Medicine in Rajarajeswari Medical College & Hospital were enrolled. The study was approved by the hospital's ethical committee

Study period: From December 2018 to May 2020 (one and a half years)

Inclusion Criteria:

1. Patients with age >40years
2. Patients diagnosed with COPD based on Global Initiative for chronic obstructive pulmonary disease (GOLD)guidelines i.e.the presence of post-bronchodilator FEV1/FVC <0.7

Exclusion Criteria:

1. Patients with active pulmonary tuberculosis.
2. Patients with bronchiectasis, bronchial asthma.
3. Patients with asthma COPD overlap

Study methods:

COPD was diagnosed based on the Global initiative for chronic obstructive pulmonary disease (GOLD) guideline. The purpose of the study was explained and informed consent was obtained. A detailed history including the number of pack years, exposure to biomass fuel, and outdoor air pollution was taken and a thorough clinical examination, relevant laboratory and specific investigations (when applicable) were done in patients, with chronic obstructive pulmonary disease (COPD).

The severity of Breathlessness was graded based on mMRC grading ranging from grade 1 to grade 4. All patients completed the CAT respiratory questionnaire. The total CAT score was calculated for each individual by summing the points for each variable The CAT has a scoring range of 0 to 40 and was classified into four groups of low, medium, high and very high based on the impact level of disease on health status.

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Comorbidities were diagnosed based on the previous medical records along with present medication and clinical and laboratory parameters relevant to the diagnosis of comorbidities at the time of enrolling for the study.

Each patient was investigated for Complete blood count, Peripheral smear, ESR, CRP, RBS, FBS, PPBS, Urea & serum creatinine, LFT, Arterial blood gas analysis, X-ray chest, LIPID PROFILES, Spirometry, TROPI, ECG, 2D ECHO based on the history and physical examination relevant for the diagnosis of comorbid diseases

Spirometry: Spirometry was performed using a heliox spirometer according to the ATS guidelines.

Follow-up: All the patients were followed up after a period of 1 year with repeat spirometry along with an assessment of the CAT questionnaire.

Statistical analysis: The quantitative variables in the present study such as age, were summarized in terms of descriptive statistics such as mean and standard deviation. All the qualitative variables, such as gender were expressed in terms of frequencies and proportions. The Chi-square test, Pearson correlation test, t-test and z-test were used to find the association between the comorbidities, systematic inflammation and COPD. SPSS Version 20 software was used for statistical analysis. P-values of less than 0.05 were found statistically significant.

Ethical consideration: Institutional Ethics Committee approval was obtained on 02nd Nov 2018 before starting the study with Reference No. RRMCH-IEC/19/2018-19. The title of the study, aim, and benefits were clearly explained in their regional language. Participants' privacy was maintained throughout the study. Participants were given the right to refuse to take part in the study at any time.

3. OBSERVATION AND RESULTS

In this retrospective study, 108 patients were included with mean age of 64.7, of which the majority belonged to the age group of 51-70 years consisting of about 75 patients(69%) & majority i.e. 99 were males(92%) and 9 were females(8%) of which 72 had exposure to agricultural dust, 10 had exposure to outdoor air pollution, 12 welding fumes. 9 patients had exposure to biomass fuel of which 3 had exposure to agricultural dust, 1 textile dust and 1 flour dust.

Table 1: Comparison of study subjects based on the presence of comorbidities and number of exacerbations

Comorbidities		Frequency of exacerbation		z test	p-value
		<=1	>=2		
Metabolic Syndrome	HTN	4	32	-6.5997	<0.00001
	DM	0	13	-5.099	<0.00001
	Dyslipidemia	5	3	1	0.31732
	Obesity	1	1	0	1
CVD	IHD	3	10	-2.7456	0.00596
	LVF	1	2	0.8165	0.41222

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	RVF	2	18	-5.0596	<0.00001
Nutritional Disorders	**Anemia**	1	13	-4.5356	<0.00001
	Polycythemia	0	2	-2	0.0455
	Malnutrition	1	17	-5.3333	0.00001
Psychiatric Disorders	**Anxiety**	4	5	-0.4714	0.63836
	Depression	3	6	-1.4142	0.155854
	GERD	5	21	-4.4376	<0.00001
	Lung cancer	0	2	-2	0.0455

Most of the patients had more than 2 exacerbations per year. Among these majority of those who had comorbidity of hypertension, diabetes mellitus, ischemic heart disease, CAD, RVF, GERD, malnutrition and anemia, polycythemia and lung cancer had a significant correlation with an increased number of exacerbations using the Chi-Square test(p-<0.05)

Table 2: Distribution of study subjects based on severity of airflow obstruction and inflammatory markers

Severity of Obstruction	**Inflammatory Markers**				**Chi Square(df)**	**p-value**
	TLC	**Neutrophils**	**CRP**	**ESR**		
Mild	1	1	2	0	21.4 (9)	0.011
Moderate	14	18	26	46		
Severe	33	23	32	38		
Very Severe	0	10	14	14		

There is a strong negative correlation of raised ESR, CRP, neutrophils and total leucocyte counts with airflow obstruction suggesting that increased inflammatory markers are associated with a decrease in FEV1 levels

Table 3: Comparison of study subjects based on comorbidities and elevated CRP levels, elevated ESR levels.

Comorbidities	**Mean**	**Raised CRP Level**				**Raised ESR Level**			
		Y	**N**	**z-test**	**p-value**	**Y**	**N**	**z-test**	**p-value**
HTN	36	24	12	2.8284	0.00466	32	4	6.5997	<0.00001
DM	13	13	0	5.099	<0.00001	13	0	5.099	<0.00001
Obesity	2	1	1	0	1	1	1	0	1
Dyslipidemia	8	8	0	4	0.00006	6	2	2	0.0455
IHD	13	9	4	1.9612	0.05	9	4	1.9612	0.05
RVF	20	17	3	4.4272	<0.00001	19	1	5.6921	<0.00001
LVF	3	3	0	2.4495	0.01428	3	0	2.4495	0.1428
Anemia	14	8	6	0.7559	0.44726	4	12	0.7559	0.44726
Polycythemia	2	2	0	2	0.0455	2	0	2	0.0455
Malnutrition	18	14	4	3.6723	0.00024	16	2	-2	0.0455
Anxiety	9	6	3	1.4142	0.15854	9	0	4.2426	<0.00001
Depression	12	11	1	4.0825	<0.00001	12	0	4.899	>0.00001
GERD	26	24	2	6.1017	<0.00001	26	0	7.2111	<0.00001
Lung Cancer	2	1	1	0	1	1	1	0	1

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The disease that showed a significant correlation with raised CRP using the Chi-Square test (p-value of >0.05) are hypertension, diabetes mellitus, dyslipidemia, IHD, RVF, LVF, Polycythemia, malnutrition, depression and GERD.

Diseases such as HTN, DM, IHD, Dyslipidemia, RVF, polycythemia, malnutrition, anxiety, depression and GERD have a significant correlation using the Chi-square test (p-<0.01)

Table 4: Comparison of study subjects based on comorbidities and elevated Neutrophil Count.

Comorbidities	Mean	Elevated Neutrophil Count			
		Y	N	z-test	p-value
HTN	36	24	12	4.64	<0.00001
DM	13	8	5	1.1767	0.238
Dyslipidemia	8	6	2	2	0.455
IHD	13	5	8	-1.4142	0.15854
RVF	20	8	12	-1.2649	0.20766
LVF	3	2	1	0.8165	0.41222
Anemia	14	11	2	3.5301	0.00042
Polycythemia	2	2	0	2	0.0455
Malnutrition	18	13	4	3.087	0.002
Anxiety	9	6	3	1.4142	0.15854
Depression	12	3	9	1.432	0.234
GERD	26	12	14	-0.5547	0.58232

Total leucocyte counts were significantly higher in COPD patients with a history of HTN, Anemia, Polycythemia, and malnutrition which had a strong positive correlation using z-test with a p-value of < 0.05

Table 5: Comparison of change in the severity of CAT score with various Comorbidities

Comorbidities		Severity of CAT score			
		CAT (baseline)	CAT (follow up)	t-statistics	p-value
Metabolic Syndrome	**HTN**	14.05±4.82	25.5±5.44	9.452	0.0001
	DM	16.23±4.901	29.2±5.165	6.56	0.0001
	Dyslipidemia	14±4.6	22.125±5.51	3.202	0.006
	Obesity	10.5±4.55	21±6.33	1.905	0.19
CVD	**IHD**	14.15±4.89	26.307±6.33	5.48	<0.0001
	LVF	14.33±5.06	25±6.73	2.195	0.09
	RVF	13.7±4.874	27.05±6.02	8.285	<0.0001
Nutritional Disorders	**Anemia**	16.28±4.88	29.92±6.42	6.329	<0.0001
	Polycythemia	15±4.94	26±6.47	1.911	0.1962
	Malnutrition	15.944±4.853	27.83±6.1	6.469	<0.0001
Psychiatric	**Anxiety**	14.66±4.87	24.5±6.114	3.777	0.0017

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Disorders	**Depression**	15.91±4.91	28±6.21	5.29	<0.0001
GERD/ Peptic ulcer		16.15±4.87	27.88±6.113	7.653	<0.0001

COPD patients with various comorbidities were evaluated for CAT scores at the time of enrollment. Patients with a history of HTN, DM, dyslipidemia, IHD, RVF, anemia, malnutrition, depression and GERD had increased CAT score as compared to baseline value after 1 year using a paired t-test with p-value of < 0.05

Table 6: Comparison of change in the severity of airflow obstruction with various Comorbidities

Comorbidities		**Severity of airflow obstruction**			
		FEV1 (baseline)	**FEV1 (follow up)**	**t-statistics**	**p-value**
Metabolic Syndrome	**HTN**	47.39±8.68	34.2±8.01	-6.69	0.0001
	DM	47.61±13.3	34.53+8.225	-3.016	0.006
	Dyslipidemia	49±12.8	40±12.1	-1.445	0.1704
	Obesity	55±14.4	38±13.8	-1.205	0.3515
CVD	**IHD**	50.15±13.1	35.07±10.56	-3.231	0.0036
	LVF	43.33±12.3	30.66±8.48	-1.469	0.2158
	RVF	49.6±12.3	36±10.02	-3.834	0.0005
Nutritional Disorders	**Anemia**	42.71±13.1	31.1±9.906	-2.645	0.0137
	Polycythemia	37±12.1	26.5±8.47	-1.005	0.4206
	Malnutrition	39.33±13.3	31.055±9.9061	-2.117	0.0417
Psychiatric Disorders	**Anxiety**	43.444±13.2	34.55±10.04	-1.588	0.1319
	Depression	39.5±13.2	30±10.156	-1.766	0.0913
GERD/ Peptic ulcer		42.38±13.2	32.38±10.059	-3.072	0.0034

COPD patients with various comorbidities were evaluated for change in the level of airflow obstruction. Patients with COPD who had a history of HTN, DM, IHD, RVF, anemia, malnutrition, depression and GERD had increased severity of airflow obstruction on follow-up as compared to baseline value using a paired t-test with p-value of <0.05. whereas the patients with comorbidities such as dyslipidemia, obesity, LVF, polycythemia and anxiety did not have a significant reduction in airflow obstruction.

4. DISCUSSION

In this study, we explored the prevalence of comorbidities, elevation of inflammatory markers and their impact on disease progression in a cohort of COPD patients.

This is a prospective study that included 108 COPD patients of which the majority in the age group of 60-80 years had moderate to severe airflow obstruction on spirometry. Therefore, the correlation between the severity of airflow obstruction and an advancing age was statistically significant. The current smoking history of the patient doesn't correlate when compared with ex-smokers for the severity of airflow obstruction which indicates the fact that systemic inflammation in COPD patients continues even after quitting smoking.

Most of the patients who had a moderate to severe obstruction had pack years of smoking of more than 20. The number of pack years has a significant correlation with the severity of

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airflow obstruction using the Chi-square test (0.0001)

Severity of airflow obstruction has a very significant positive correlation with the CAT score. The most prevalent co-morbidities were Hypertension seen in 36 patients, followed by GERD in 26, RVF in 20, malnutrition in 18, Anemia in 14, IHD in 13, DM in 12, depression in 9, anxiety in 9, Dyslipidemia in 8. The least prevalent among them were LVF in 3, polycythemia in 2, and obesity in 1.

The majority of the patients had more than 2 exacerbations per year. Among these comorbidity of hypertension, diabetes mellitus, ischemic heart disease, RVF, GERD, malnutrition and anemia, polycythemia and lung cancer had significant correlation with an increased number of exacerbations(p-<0.05).

Diseases such as HTN, DM, IHD, Dyslipidemia, RVF, polycythemia, malnutrition, depression and GERD has a significant correlation with raised ESR and CRP using Chi-square test (p-<0.01).

Patients with COPD who had a history of HTN, DM, dyslipidemia IHD, RVF, anemia, malnutrition, depression and GERD had increased severity of airflow obstruction after one year of follow-up as compared to the baseline value.

Our study shows a strong negative correlation of raised ESR, CRP, neutrophils and total leucocyte counts with airflow obstruction suggesting that increased inflammatory leads to decrease in FEV1 levels and CAT score associated with decreased quality of life

5. CONCLUSION

In conclusion, COPD is frequently associated with various co-morbidities such as Hypertension, Diabetes mellitus, ischemic heart disease, GERD, and malnutrition with consistent evidence that these co-morbidities have a great negative impact on COPD patients in terms of exacerbation, worsening airflow obstruction, health status and severity of dyspnea. Hence early detection and treatment of these comorbidities in COPD patients can prevent the development of complications in them due to the combined effect of both diseases. Management of medical intervention in COPD patients with co-morbidities needs a holistic approach that is not clearly established in guidelines worldwide. All healthcare specialities need to work together to provide multidisciplinary treatment strategies for COPD patients.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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