International Journal of Sciences & Applied Research

www.ijsar.in

Various co-morbidities and prevalence of co-morbidities in Chronic Obstructive Pulmonary Disease (COPD) reporting to tertiary care center

Rajendra Saugat[1]*, Deepak Katker[1], Tarun Baid[1], Manak Gujrani[1], Gunjan Soni[1], Saroj kumari[3], Chandra Shekhar Modi[2], Akhil kapoor[3]

[1]Department of Respiratory Medicine, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, India.
[2]District Tuberculosis Officer, Bikaner, Rajasthan, India.
[3]Department of Radiation Oncology, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, India.
Correspondence Address: * Rajendra Saugat, Department of Respiratory Medicine, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, India.

Abstract
It is now well known that COPD is associated with significantly systemic abnormalities such as ischemic heart disease, lung cancer, anemia osteoporosis, Diabetes, hypertension, Depression, and various other co morbidities. The inflammatory processes in COPD contribute to remodeling of pulmonary tissues; the same inflammatory processes that characterize COPD are also risk factors for these co-morbidities. Patients (78.5%) were in 41-70 years age group with severe (39.2%) and very severe (48%) COPD mostly from rural, illiterate and smoker.

Keywords: COPD, systemic inflammation, inflammatory marker, Co-morbidities, smoking, Dyspnea

Introduction

Chronic Obstructive Pulmonary disease traditionally has been considered a disease of the lungs, secondary to smoking and pollution characterized by airflow obstruction due to abnormalities of both bronchia and lung parenchyma which is not fully reversible with bronchodilator[1]. The WHO predicts that by 2020 COPD will rise from its current ranking as 12th most prevalent disease worldwide to the 5th and from 6th most common cause of death to the third[2, 3]. The prevalence of COPD in India is 5% in males and 2.7% in females. It is now well known that COPD is associated with significantly systemic abnormalities such as ischemic heart disease, lung cancer[4,5,6], anemia osteoporosis, Diabetes, hypertension, Depression[7], and various other co morbidities. In COPD patient there is increased level of systemic inflammation and increased level of inflammatory marker causes bad effect and generate many co-morbid condition[8,9]. COPD patients die more due to co-morbidities then itself. Co-morbidities are defined as "Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study." The inflammatory processes in COPD contribute

to remodeling of pulmonary tissues, leading to the irreversible airflow limitation characteristic of this disease because there is increasing evidence that COPD is a more complex systemic disease than an airway and lung disease, The same inflammatory processes that characterize COPD are also risk factors for these co-morbidities, systemic inflammation, systemic oxidative stress, marked changes of vasomotor and endothelial function and enhanced circulating concentrations of several pro-coagulant factors. The inflammatory processes in COPD contribute to remodeling of pulmonary tissues, leading to the irreversible airflow limitation characteristic of this disease. Inflammation may also contribute to the co-morbidities often observed in COPD patients. Malnutrition can arise from primary (inadequate or poor-quality food) or secondary causes are diseases itself. Malnutrition[10,11,12] is a cause of loss of body cell mass and associated with a reduction in the mass of the diaphragm and respiratory muscles, resulting in declines in strength and endurance. Malnutrition decline in immune status, elevated concentrations of soluble tumor necrosis (TNF) and TNF is associated with cachexia, anorexia **A**nemia and Poly-cythemia in COPD patient, anemia results from several factors, including a slightly shortened RBC survival, reduced iron utilization, and an impaired bone marrow erythropoietic response. Osteoporosis characterized by low bone mass and micro architectural deterioration of bony tissue leading to enhanced bone fragility and a consequent increase in fracture risk, in COPD, increased risk of osteoporosis because of their age, limited physical activity, low BMI, smoking, hypo-gonadism , malnutrition, and use of corticosteroids.

Metabolic changes in COPD (diabetes mellitus, Dyslipidemia), metabolic syndrome[13] (syndrome X, insulin resistance syndrome) as in COPD smoking has been established as a risk factor for diabetes, TNF-a, IL-6, and CRP, which are elevated in COPD, are also increased in diabetes ,reduced lung function and prolong use of steroid as a risk factor for the development of diabetes, increase in low-density lipoprotein (LDL)-C, triglycerides, and very low-density lipoprotein (VLDL)[14,15,16], Disturbances of respiratory function that cause pulmonary hypertension(>30mmhg) include diffuse parenchymal lung diseases that impair gas exchange and elicit chronic hypoxia (e.g. COPD, IPF), elevated circulating levels of the pro-inflammatory cytokine interleukin-6 (IL-6) and C-reactive protein directly correlated with elevations in mPAP ($r = 0.39$; $P < 0.001$).Cor-pulmonale is an enlargement of the right ventricle due to derangements in the structure or function of the respiratory system, In response to the increased PVR the right ventricle (RV) gradually undergoes hypertrophy and dilatation, true right heart failure is characterized by raised jugular venous pressures, congestive hepatomegaly, and peripheral edema. COPD symptoms that increase the risk for anxiety and depression, hopelessness[17]. A study conducted in the UK, published in the European Respiratory Journal, investigated 169 COPD patients over a one year period, repeated exacerbation and hopelessness is main cause of Depression.

Material and Method

This was a cross sectional study of COPD patients. Diagnosis of COPD was based on clinical presentation dyspnea (Table-1) and spirometry (Table-2) as by Gold criteria's. Patients were include on following criteria's, patients age were >40 year and clinical stable with acceptable performance of spirometry, history of smoking (Packs/Year = No. of cigarettes/Bidi smoked/day x No of years smoked/ 20) and exposure to other biomass fuel, clinical features suggestive of COPD, spirometry FEV_1/FVC <70 %(Post bronchodilator) and chest radiography. Patients were excludes, those patients are

seriously ill, lactating mother and pregnant women, pulmonary TB patients .Other related investigation also done e.g. Complete blood counts ,ESR, Blood sugar, Blood urea, sr.creatinine ,serum bilirubin, SGOT, SGPT, Alk Phosphatase, Serum protein, Serum albumin, 12 lead standard electrocardiogram(ECG), Postero-anterior plain chest roentgenogram, Spirometry, 2D-ECHO, Bone Mineral Density, Optional investigations were USG abdomen , HRCT/CECT –Chest, Lipid profile, Fiber-optic Bronchoscopy, FNAC.

Assessment of Dyspnea: Modified Medical Research Council Scale (MMRC).

Table 1: MMRC Dyspnea Scale[1]

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

Table 2: The stages of COPD as per the GOLD criteria (2010)[1].

Stage	Severity	
I	Mild COPD	$FEV_1/FVC<0.70$ $FEV_1 \leq$ 80% Predicted
II	Moderate COPD	$FEV_1/FVC<0.70$ $50\% \leq FEV_1 < 80\%$ Predicted
III	Severe COPD	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ Predicted
IV	Very Severe COPD	$FEV_1/FVC < 0.70$ $FEV_1<30\%$ predicted or $FEV_1 < 50\%$ plus chronic Respiratory failure

FEV_1: Force expiratory volume in one second; FVC: Forced vital capacity

Diagnosis of various co-morbidities of COPD was based on following criteria.

Malnutrition[18]":BMI= weight (kg)/ height ($meter^2$).Low<18.5, Normal18.5-24.99, overweight 25-29.99, Obese>30. Triceps skin fold thickness <3mm, Serum Albumin <3.5gm/dl.

Anemia[19]: WHO criteria of a hemoglobin (HGB) <13g/dl (<130g/l) in men and <12g/dl (<120g/L) in women have been used to define anemia.

Polycythemia[19]: Hemoglobin >18gm/dl

Depression[20] persistent sadness or low mood; and/or, loss of interests or pleasure, fatigue or low energy (at least one of these, most days, most of the time for at least 2 weeks, if any of above present, ask about associated symptoms disturbed sleep, poor concentration or indecisiveness, low self-confidence, poor or increased appetite, suicidal thoughts or acts, agitation or slowing of movements, guilt or self-blame.

Diabetes Mellitus[20]: Symptoms of diabetes plus random blood glucose concentration 11.1mmol/L (200mg/dl) or, fasting plasma glucose 7.0mmol/L (126mg/dl) or, two hour plasma glucose 11.1 mmol/L (200mg/dl) during an oral glucose tolerance test.

Systemic Hypertension[21]: Hypertension (defined as any one of the following: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg.

Pulmonary Hypertension & Corpulmonale[21]:
Physical Examination(Pedal Edema, neck vein engorgement, Hepatomegaly, ECG, Right axis deviation ,R or R'>S in V1 ,R < S in V6,R in Vq+S in V5 or V6 = 10mm,R in V1 = 7mm,R in V1 = 15mm with right bundle branch block, Right atrial enlargement,2D-ECHO : Mean pulmonary artery pressure greater than 25 mmHg at rest, or greater than 30 mmHg with exercise.

Left Ventricular Failure[21]:
2D-ECHO,Hyperdynamic corresponds to LVEF greater than 70%,Normal Corresponds to LVEF 50% to 70% (mid point 60%),Mild dysfunction Corresponds to LVEF 40% to 49% (midpoint 45%),Moderate dysfunction : Corresponds to LVEF 30% to 39% (midpoint 35%),Severe dysfunction: Corresponds to LVEF less than 30%.

Left Ventricular Diastolic Dysfunction[21]: 2D-ECHO.

Metabolic Syndrome: IDF Criteria for the Metabolic Syndrome (Central Adiposity), Waist circumference Men (>90cm), Women (>80cm), plus any two of the following**:** Fasting triglycerides >150 mg/dl or specific medication, HDL cholesterol <40 mg/dl and <50 mg/dl for men and women, respectively, or specific medication, Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication, Fasting plasma glucose ≥100 mg/dl or previously diagnosed Type 2 diabetes.

Osteoporosis & Osteopenia[22,23] : Diagnosis of demineralization was done by using pronosco X-posure software based method after doing X-ray hand (AP-View). With Pronosco X-posure V.2 based on DXR, a BMD estimate is obtained through a combined computerized radiogrammetric analysis and textural analysis of radiograph of hand. Information from the middle three metacarpals is used by system to generate a BMD estimate. This is referred as digital X-ray radiogrammetry BMD (DXR-BMD). T score of less than -1.0 being defined as osteopenic and a T score of less than -2.5 being referred as osteoporotic.

WHO Criteria for Osteoporosis[24]: Normal BMD < 1 SD below youngadult reference range, High BMD > 2.5 SD below young adult reference mean, Severe Osteoporosis BMD > 2.5 SD below young adult reference mean, plus 1 or more fragility fractures Osteopenia BMD 1-2.5 SD below young adult reference range

Timely identification and appropriate management of co-morbidities across existing boundaries of expertise are likely to benefit patients. Therefore it is essential to take holistic and patient centered view when accessing patients with COPD

Observation
To know various co-morbidities of COPD and its prevalence. Study was also done to know correlation of COPD co-morbidities with stages of COPD, age group 61-70 years were in stage IV (53.5%) and stage III (34.9%) 1.2 in present study 102 patients were enrolled, 98 were males and only 4 were females. Maximum cases were in stage IV (48%) and stage III (39.2%), majority of patients belongs to rural area (n=73) 71.8% and 28 (28.2%) to urban, HDL they are in stage IV (45.2%) and stage III (42.5%) of COPD. 48.3% were farmers and they were in stage IV (42.9%) and stage III (44.9%). 19.6% were laborers and 60% were in stage IV and 25% in stage III.. Out of total 102 patients 74 patients had their duration of illness ≤5 years and maximum patients

were in spirometry stage, III and IV ,in 102 COPD patients, Breathlessness was present in all 102(100%) cases ,cough in 69(67.7%) cases, expectoration were present in 55(53.9%), weakness in 38(37.3%), loss of interest in surrounding in 35(34.3%), loss of appetite in 33(32.3%), feeling hopeless/depressed in 32(31.4%), chest pain in 19(18.6%), loss of weight in 18(17.7%),chest tightness in 7(6.9%) pedal swelling in 15(14.7%), fever in 8(7.8%),wheezing in 5(4.9%),hemoptysis 3(2.9%), increased thirst and increased frequency of micturation in 1(1%) each**.** according to MMRC Scale dyspnoea were in grade III (n=48) follow by grade IV, II and I, as 100% patients having dysnoea.. Hypertension was present in 25(24.5%) patients Along with COPD of stage III and IV, H/O hospitalization was present in 21 patients and most of were in spirometric IV, depression was present in 22(20.6%) patients and maximum in spirometric IV. diabetes was present in 18(17.7%) cases and in spirometric stage IV,. Recurrent respiratory tract infection was present in 12(11.8%) cases and maximum were in stage IV i.e. 8(66.7%). maximum patients were (71.6%) illiterate and maximum in stage IV.11 Out of total 102 patients, 95.1% patients were smokers rest of non smokers. 102 patients were having inhalational exposure to Bidi (87.3%), chilam (23.5%), cigarette (10.8%) and hukka (4.9%). And maximum patiens were in spiromertric stage found in III and IV,(Some patients were taking more than one inhalational mode of tobacco smoke so total of above table is not 102.) Maximum number of COPD patients used to 30- 40 packs/year. Other then smoking, 71(69.6%) patients develop COPD due to indirectly exposed to biomass fuel while 13 patients due to exposed passive smoking. Only 4 patients due to directly exposed to biomass fuel. majority of cases (n=50) had their BMI <18.5 (underweight) and found in spirometric stage, III and IV , Out of 102 patients 22 (21.6%) were found hypertensive (systolic BP $\geq$140mmHg) and mostly in spirometric stage, III. In present study, general physical examination shows, <3mm triceps skin fold thickness, Barrel shaped chest, , pedal edema, neck vein engorgement, pallor was found in COPD patients in spirometric stage III and IV. On statistical comparison the difference was insignificant ($p>0.05$) for all general physical examination.19 here we find 88 patients were using DPI and 3 patients were using MDI devices for COPD treatment in Bikaner zone. And co-morbidities were present in 96(94.12%) patients**.** In present study co-morbidities were, anemia in53.9%, poly cyathemia in 2(1.9%) patients. osteopenia in 18 patients, and osteoporosis in 12 patients, 54(52.9%) patients were malnourished, while 3 patients had metabolic syndrome. pulmonary hypertension in 38(40.9%) patients while LV diastolic dysfunction in 20(21.5%) patients, LVF was present in 24(25.8%) patients, lung cancer, Systemic hypertension, Diabetes and Depression was present in 6, 25, 17 and 35 patients respectively. 55 anemic patients and polycyathemia in 2 patients were in spirometric stage IV, 18 osteopeniac patients , 12 osteoporosis patients,. 1 each metabolic patients ,38 pulmonary hypertension patients, LV diastolic dysfunction in 21.5% (n=20) cases, LVF were in 25.8% and, Lung cancer were present in only 6 patients and out of them 2 in each stage. Hypertension was present in 25 (24.5%) cases and, diabetes were present in 17 (16.7%) cases , depression were present in 35(34.3%) most of co-morbidities present in spirometric stage, III and IV .In present study, 102 patients were enrolled, 309 co-morbidities were found and each patient had 3 co-morbidities.

Discussion

In our study, Total 102 patients were enrolled on OPD visit and comprising majority of males 98(96.1%) and few

females 4(3.9%). Out of 98 males, 47 males (48%) were in stage IV, 38(38.8%) in stage III, 12(12.2%) in stage II, only 1 male (1%) in stage I and out of 4 females 2(50%) were in stage IV and 2(50%) in stage III. This shows that COPD is more prevalence in males than females and majority of patients reported were in stage III and IV[25], which has been attributed to the historically higher rates of cigarette smoking in males. Majority of enrolled patients were between 61-70 years age group (42.2%) and maximum patients were in stage IV (53.5%) and stage III COPD (34.9%). This shows that COPD is more common in older age[26,27]. Majority of patients were from rural area (71.8%) than urban area (28.2%) and patients were found in stage IV (45.2%) and stage III (42.5%), urban patients maximum were in stage IV (55.2%) and stage III (31%). In rural population, habits and duration of tobacco smoking is higher than urban population[28,29-30].Farmers are more enrolled and have more common COPD with severe form of COPD then urban people with other occupation. Farmers with atopy appear more susceptible to develop farming related COPD[31]. Maximum patients were suffering from long duration 5 years (72.6%) of disease, and COPD were found in stage IV (48.6%) and stage III (36.5%). Every patient was breathlessness at the time of presentation and most of them found in stage IV (48%) and stage III (39.2%) of COPD. According to MMRC scale, dyspnea were in grade III (47.1%), grade IV (38.2%), and higher grade of dyspnea was associated with severe COPD (stage IV; 64.1%), stage III (33.3%).Grades of dyspnea are directly proportional to stages of COPD Mahler et al[32]. Second most common symptoms were cough (67.7%) with expectoration (53.9%) at the time of presentation, most patients were (71.6%) illiterate and they had stage IV (45.2%) and stage III (39.7%).Now it is well known that Smoking is most common cause of COPD and in India most common mode of smoking is BIDI[33] (95.09%), ,Chilam (23.5%), cigarette (10.8%), Hukka (4.9%). Maximum BIDI smokers were in stage IV (49.4%) and stage III (37.1%). ,chilam smokers patients were found in stage III (50%) and stage IV (41.7%). Bidi is more harmful than cigarettes in term of having more nicotine, tar and number of puff smoked each time compared to cigarettes[34] and maximum patients were having history of >40 pack years of smoking (34.8%), were found in stage IV (19.1%) & stage III (12.4%),here we found that Pack year of smoking are directly proportional to stages of COPD[35,36] Apart from smoking, biomass fuel exposure were 69.9%, 8.82% were passive smoking; biomass fuel and passive smoking also enhance development of COPD. Subjects exposed to indoor air pollution due to burning of biomass in poorly ventilated dwellings prevalent in rural settings and in farmers, COPD develops at higher rate in them than in others, especially in females[37].stage IV (51.9%) and stage III (40.7%) were associated with low BMI (18.5),decrease triceps skin fold thickness (<3mm) and malnutrition . lower BMI (i.e. <21 kg/m^2) is associated with greater risk of mortality and co-morbidities[,38,39,40],COPD have better prognosis if they are normal or overweight, barrel shaped chest present in 48% and were found in stage IV (27.5%) ,III (14.7%). In total enrolled (102) patients 89.2% patients were using inhalational mode of treatment. Co-morbidities were present in patients (94.1%), National health and Nutrition examination Survey (NHANES) [41]. In our study, anemia present in highest (53.9%),malnutrition (52.9%), pulmonary hypertension (40.9%), depression (34.31%), left ventricular failure (25.8%), systemic hypertension (24.5%), left ventricular diastolic dysfunction (21.5%), osteopenia (19.6%), diabetes (16.7%), osteoporosis (13%), lung cancer (5.9%), metabolic syndrome (2.9%), polycyathemia (1.9%). Pedal edema (19.6%) and neck vein engorgement was present in 21.6% 20%

patients were suffering from corpulmonale most of co-morbidities present in higher stage of COPD. Molen in the year 2010 found that depression was having prevalence of 10-42% in COPD patients; depression is "more prevalent in people with COPD than in people with other chronic conditions[42]. 45.5%cases of anemia were found in stage III. Cause of anemia were erythropoietin resistance, other factors are probably involved in the pathogenesis of anemia in these patients[43], diabetes mellitus (16.7%) were found in stage IV, type 2 diabetes is more prevalent in moderate to very severe COPD than in the general population, with an overall prevalence of 12.7% in the combined ARIC and CHS cohorts[44]. systemic inflammation was more intense in COPD patients with metabolic syndrome than without metabolic syndrome, lung cancer (5.9%) was equally present in all stages.

Summary and Conclusion

In this study102 patients enrolled, 98 male and 4 females, rural 71.8% and urban28.2%,farmers(40.03%),71.6%illetirate,(95.09%) were smokers(Bidi 87.3%, chilam (23.5%), cigarette (10.8%), Hukka (4.9%). ,they(78.5%) were in 41-70 years age group with severe (39.2%) and very severe (48%) COPD according to spirometric stages.71.8% patients were from rural area as compared to urban area (28.2%). Average duration of disease between 1-5 years, Symptoms were 100%Breathlessness MMRC scale (47.1% in grade III,38.2% in grade IV, cough (67.7%) and cough with expectoration (53.9%), Apart from smoking, 69.6% male were indirectly,100% female directly exposed to biomass fuel. Majority of patients of COPD were having one or more co morbid conditions in 94.11% patients, Pulmonary hypertension (40.9%), Left ventricular diastolic dysfunction (21.5%), Left ventricular (25.8%). Systemic hypertension (24.5%).

Relation of Comorbidities of COPD to Spirometry stages of COPD

Comorbidities	**Spirometry Stages**								**Total**	
	I		**II**		**III**		**IV**			
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Anaemia	1	1.8	5	9.1	25	45.5	24	43.6	55	53.9
Polycyathemia	0	-	0	-	0	-	2	100	2	1.9
Osteopenia	0	-	3	16.7	7	38.9	8	44.4	18	19.6
Osteoporosis	0	-	1	8.3	1	8.3	10	83.3	12	13.0
Malnutrition	0	-	4	7.4	22	40.7	28	51.9	54	52.9
Metabolic Syndrome	0	-	1	33.3	1	33.3	1	33.3	3	2.9
Pulmonary Hypertension	1	2.6	1	2.6	12	31.6	24	63.2	38	40.9
LV Diastolic Dysfunction	0	-	1	5.0	9	45.0	10	50.0	20	21.5
LVF	0	-	2	8.4	14	58.3	8	33.3	24	25.8
Lung Cancer	0	-	2	33.3	2	33.3	2	33.3	6	5.9
Hypertension	0	-	4	16.0	12	48.0	9	36.0	25	24.5
Diabetes	0	-	4	23.5	5	29.4	8	47.1	17	16.7
Depression	0	-	4	11.4	10	28.6	21	60.0	35	34.31
Total	2	0.6	32	10.4	120	38.8	155	50.2	309	
Mean	0.15±0.38		2.46±1.61		9.23±7.89		11.92±9.18		5.94±7.66	

Prevalence of anemia (53.9%) highest, Malnutrition (52.9%), Depression (34.3%) Demineralization of bone (32.6%) cases in which osteoporosis 13% cases while osteopenia 19.6% cases. Diabetes mellitus (16.7%), Metabolic syndrome (2.9%), Lung cancer (5.9%), Polycyathemia (1.9%) cases found in stage IV (100%).In present study, total 309 co-morbid conditions were present in 102 patients. So on an average 3 co-morbidities present in 1 patient. Maximum number 155 (50.2%) of co-morbidities were present in stage IV (very severe COPD) which is followed by stage III (severe COPD, 120(38.8%), stage II (moderate COPD) (10.4%) and stage I (mild COPD) (0.6%).

References

1. GOLD strategy for diagnosis, management and prevention of chronic pulmonary disease. Executive summary update 2010.
2. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 1998; 157(5) : 1418–1422.
3. Huertas A, Palange P. COPD www. Medscape.com/viewarticle/ 744076.
4. Malhotra S, Lam S, Man SF, Gan WQ, Sin DD. The relationship between stage 1 and 2 non-small cell lung cancer and lung function in men and women. BMC Pulm Med 2006;6:2.
5. Nomura A, Stemmermann GN, Chyou PH, Marcus EB, Buist AS. Prospective study of pulmonary function and lung cancer. Am Rev Respir Dis 1991;144:307–311.
6. Papi A, Casoni G, Caramori G, Guzzinati I, Boschetto P, Ravenna F, Calia N, Petruzzelli S, Corbetta L, Cavallesco G, et al. COPD increases the risk of squamous histological subtype in smokers who develop non-small cell lung carcinoma. Thorax 2004; 59 : 679–681
7. PMA. Neuropsychological deficits in chronic J. Hyg Environ Health 2003; 206: 279-89.
8. Anant R, Patel C, Hurst JR. Extrapulmonary Comorbidities in Chronic Obstructive Pulmonary Disease: State of the art CME www.medscape.org/viewarticle/750112.
9. Engelen MPKJ, Schols AMWJ, Lamers RJS, Wouters EFM. Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. Clin Nutr 1999; 18 : 275–80.
10. Engelen MPKJ, Schols AMWJ, Does JD, Wouters EFM. Skeletal muscle weakness is associated with wasting of extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 2000; 71 : 733–8.
11. Schols AMWJ, Slangen J, Volovics L, Wouters EFM. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 157 : 1791–7.
12. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999; 160 : 1856–61.
13. Schols AMWJ, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax 1996; 51 : 819–24.
14. Engstrom G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L. Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. J Intern Med 2003; 253 : 574–581.

15. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM, Insulin Resistance Atherosclerosis Study. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes 2002; 51 : 1131–1137.
16. Cote C, et al. Haemoglobin level and its clinical impact in a cohort of patients with COPD. Eur Respir J 2007; 29 : 923-29.
17. Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. Eur Respir J 2003;22:809–814.
18. Landi F, Pistelli R, Abbatecola AM, Barillaro C, Brandi V, Lattanzio F. Common geriatric conditions and disabilities in older persons with chronic obstructive pulmonary disease. Curr Opin Pulm Med. 2011 ; 17 Suppl 1 : S29-34
19. Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, Garau J. Mortality after hospitalization for COPD. Chest 2002; 121 : 1441–1448.
20. Baker EH, Janaway CH, Philips BJ, Brennan AL, Baines DL, Wood DM, Jones PW. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax 2006; 61 : 284–289.
21. Han LK, McLaughlin VV, Criner GJ, Martinez FJ. Cardiovascular involvement in general medical condicitons. Circulation 2007; 116 : 2992
22. Engelen MPKJ, Wouters EFM, Deutz NEP, Menheere PPCA, Schols AMWJ. Factors contributing to alterations in skeletal muscle and plasma amino acid profiles in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 2000; 72 : 1480–7.
23. Chambellan A. et al. Prognostic Value of the Hematocrit in Patients with Severe COPD Receiving Long-Term Oxygen Therapy. Chest 2005; 128 : 1201-1208.
24. Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. Eur Respir J 2003;22:809–814.
25. Oongo, Fauci, Kasper, Hauser, Jameson, Loscalzo. Malnutrition and Nutritional Assessment. In: Harrison's Principle of Internal Medicine 18th edi 2012 pp 605-611
26. Malik SK. Profile of chronic bronchitis in North India. The PGI experience (1972-1985). Lung India 1986; 4 : 89-100.
27. Jindal SK. A field study on follow up at 10 years of prevalence of chronic obstructive pulmonary disease and peak expiratory flow rate. Ind J Med Res 1993; 98 : 20-26.
28. Ray D. A 5-year prospective epidemiological study of chronic obstructive pulmonary disease in rural south India. Ind J med res 1995; 101 : 238-244.
29. Eduard W, Pearce N, Douwes J. Chest 2009; 136 : 716-725.
30. Mahler DA. People with COPD. Proceedings of the American Thoracic Society 3(3) : 234-8.
31. Burrows B et al. Chronic obstructive lung disease II. Relationship of clinical and physiological findings to the severity of airways obstruction. Am Rev Respir Dis 1965; 91 : 665-78.
32. Beniwal S, Sharma BB, Singh V. What we can say: Disease illiteracy. JAPI 2011; 59 : 1-5.
33. Rickert WS. Determination of yields of tar, nicotine, carbon monoxide from Bidi Cigarette. Final report Ontario, Canada; Labstat Interantional Inc 1999.
34. William M. Chronic bronchitis and emphysema. In : Crofton and Douglas Respiratory Disease. Seaton A, Seaton

B, Gordon LA (Eds) 5th edi London Blackwell Sciences Publishers 2000; 1 : 616-679.
35. Joshi JM. Chronic obstruction pulmonary disease. Knowing what we mean, meaning what we say. Ind J Chest Dis Allied Sci 2008; 50 : 89-95.
36. Behara D, Jindal SK. Respiratory symptoms in Indian women using domestic cooking fuels. Chest 1991; 100 : 385-388.
37. Celli B, Cote CG, Marin JM, Casanova C, Moontes de Oca M et al. The body mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004; 350 : 1005-1012.
38. van der Molen T. Comorbidities of COPD in primary care: frequency, relation to COPD and treatment consequences. Primary Care Respir J 2010; 19(4) : 326-334.
39. Smart BA. When Asthma and COPD coexist. http://www.copdinternationa.com/library/asthma-coexist.htm.
40. Schnell K, Weiss CO, Lee T, Krishnan JA, Leff B, et al. The prevalence of clinically relevant comorbid conditons in patients with physician diagnosed COPD : a cross sectional study using data from NHANES 1999-2008. Pulmonary Medicine 2012; 12 : 26-34
41. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Eur Respir J. 2008; 32(5) : 1371-85.
42. Malerba M, Romanelli G. Early cardiovascular involvement in chronic obstructive pulmonary disease. Monaldi Arch Chest Dis 2009; 71(2) : 59-65.
43. Richmond JA, Kiss JE. Anemia in COPD: the role of blood transfusion. http://www.itxm.org/tmu/tmu2008/2008ISSUE4.pdf
44. Anant RC, Hurst JR. Extrapulmonary comorbidities in COPD: State of the art CME. CME Released: 09/28/2011; valid for credit through 09/28/2012.