An Observational Study to Asses the Echocardiographic Changes in Chronic Obstructive Pulmonary Disease

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Abstract: *Cardiovascular complications are frequent cause of morbidity and mortality in COPD. They are most profound and reproducible clinical findings associated with COPD. Roughly 30% of patients die from a cardiovascular complications. A better understanding of the association between COPD and cardiovascular complications should help improve the outcome, particularly if cardiovascular complications could be identified earlier and/or prevented. There are only few studies done in our country to assess the cardiovascular parameters in COPD. Previous echocardiographic studies in COPD present limitations because of their retrospective design, their reduced number of subjects, their partial echocardiographic analysis or their potential selection biases. To overcome these difficulties, we have prospectively explored COPD patients at a well - defined and relevant time - point of their clinical evolution, i. e. their first hospital admission due to an exacerbation, selecting them from the population admitted during a defined period of time and study is the representative of patients with clinically relevant COPD.*

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not entirely reversible. Chronic obstructive pulmonary disease (COPD) includes emphysema, an anatomically bronchitis, a clinically defined condition with chronic cough and phlegm; and small airway disease, a situation in which small bronchioles are contracted. [1]

COPD affects pulmonary blood vessels, right ventricle, as well as left ventricle leading to development of pulmonary hypertension, cor pulmonale, right ventricular dysfunction, and left ventricular dysfunction too. Echocardiography provides a rapid, noninvasive portable and accurate method to evaluate the right ventricle function, right ventricular filling pressure, tricuspid regurgitation, left ventricular function and valvular function. [2]

COPD is a leading cause of death and disability worldwide. According to World Bank data it is expected to move from its status in 2000 as the 4th and 12th most frequent cause of mortality and morbidity, respectively, to the 3rd and 5th leading cause of mortality and morbidity, respectively, in 2020. [3], [4] Cigarette smoking is the principal risk factor

for COPD. Occupational and environmental exposures to chemical fumes, dusts, and other lung irritants account for 10% to 20% of cases. [5]Individuals with a history of severe lung infections in childhood are more likely to develop COPD. [5] Alpha - 1 antitrypsin deficiency is a rare cause of COPD but should be suspected in persons in whom emphysema develops before the age of 40 or those who lack the common risk factors. [6].

COPD is a slowly progressing disease with a long asymptomatic phase, during which lung function continues to decline. Persistent cough, particularly with mucus production, is a common symptom. Dyspnea, especially with exercise, wheezing, and chest tightness may also be present. Patients often present with the first acute exacerbation of COPD at an advanced stage. Symptoms do not usually occur until forced expiratory volume in 1 second (FEV1) is approximately 50% of the predicted normal value. [7] defined condition characterized by destruction and elaboration of the lung alveoli; chronic As the disease progresses, exacerbations may become more frequent and life - threatening complications may develop. End - stage COPD is characterized by severe airflow limitation, severely limited performance, and systemic complications.

Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for Classification of severity of airflow limitation in COPD: In pulmonary function testing, a post - bronchodilator FEV1/FVC ratio of <0.70 is commonly considered diagnostic for COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) system categorizes airflow limitation into stages. In patients with FEV1/FVC <0.70:
GOLD 1 - mild: FEV1≥ 80% predicted.
GOLD 2 - moderate: 50% ≤ FEV1 < 80% predicted. GOLD 3 - severe: 30% ≤ FEV1 < 50% predicted.
GOLD 4 - very severe: FEV1 <30% predicted.

The GOLD guideline uses a combined COPD assessment approach to group patients according to symptoms and previous history of exacerbations. Symptoms are assessed using the Modified British Medical Research Council (mMRC) or COPD assessment test (CAT) scale. These can be found in the GOLD guidelines.

Group A: low risk (0 - 1 exacerbation per year, not requiring hospitalisation) and fewer symptoms (mMRC 0 - 1 or CAT <10)
Group B: low risk (0 - 1 exacerbation per year, not requiring hospitalisation) and more symptoms (mMRC≥ 2 or CAT≥ 1)
Group C: high risk (≥2 exacerbations per year, or one or more requiring hospitalisation) and fewer symptoms (mMRC 0 - 1 or CAT <10)
Group D: high risk (≥2 exacerbations per year, or one or more requiring hospitalisation) and more symptoms (mMRC≥ 2 or CAT≥ 10).
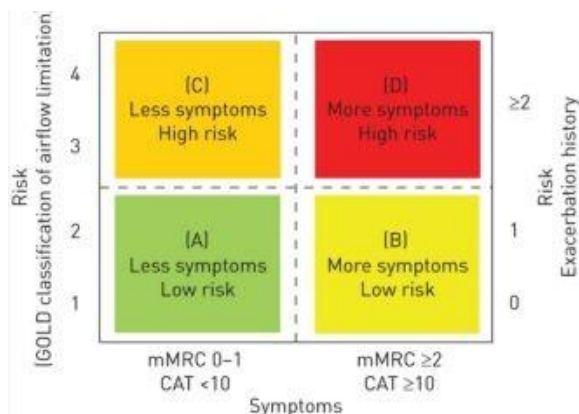
The assessment of COPD is required to determine the severity of the disease, its impact on the health status and the risk of future events (e. g. exacerbations, hospital admissions or death) and this is essential to guide therapy.

Assessment of COPD is achieved by considering the patient's current symptoms, the severity of spirometric abnormality, the exacerbation risk and the presence of comorbidities separately. [8] [9]

COPD affects pulmonary blood vessels, right ventricle, as well as left ventricle leading to the development of pulmonary hypertension (PH), cor - pulmonale (COR - P), right ventricular dysfunction, and left ventricular dysfunction. [10]

Many studies have confirmed that echocardiographically

derived estimates of pulmonary arterial pressure co - relate closely with pressures measured by right heart catheter (r> 0.7). [11], [12]

Corpulmonale (COR - P) is defined as an alteration in the structure and function of the right ventricle caused by a primary disorder of the respiratory system. PH is the common link between lung dysfunction and the heart in COR - P. [13]

Left ventricular systolic dysfunction (LVSD) is a disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and end - diastolic volume. Left ventricular diastolic dysfunction (LVDD) is defined as the inability of the ventricle to fill to a normal end - diastolic volume, both during exercise as well as at rest, while left a trial pressure does not exceed 12 mmHg. [14, 15, 16] LVDD is a common co - phenomenon in COPD. [17, 18]

2. Aims and Objectives

Aim

Correlation between Echocardiographic findings and severity of COPD.

Objectives

1) To study the Echocardiographic findings in COPD.
2) To correlate Echocardiographic findings in assessing the severity of the disease.

3. Materials and Methods

Study Area: All relevant patients visiting out - patient and in - patient of the Department of General medicine at Ramkrishna Care Hospital, Raipur, Chhattisgarh.

Study Population
The patients coming to the Department of General medicine at Ramkrishna Care Hospital, Raipur, Chhattisgarh satisfying the inclusion and exclusion criteria & who give consent to the study and who are diagnosed as chronic obstructive pulmonary disease, as per the GOLD criteria.

Inclusion Criteria:
1) Males and females Age > 18 years to <82 years.
2) Newly diagnosed cases and old follow up chronic obstructive pulmonary disease.

Exclusion Criteria
1) Patients with known sleep apnea.
2) Patients with known lung cancer and other debilitating cancers.
3) Patients with pulmonary embolism, Cerebrovascular accidents.
4) Patients with active pulmonary Koch's.
5) Patients with significant valvular heart disease, coronary artery disease (angina, Ischemic changes in resting ECG or documented history of myocardial infarction). examination could not performed.
6) Patients who were unable to perform spirometry.7.

Patients with known case of bronchial asthma.

7) Patients with very poor echogenic subjects in whom meaningful echocardiographic evaluation can be done.

Study Design: Prospective Observational study.

Study Period: 01.03.2021 - 31.11.2022

Study Site: Ramkrishna Care Hospital, Raipur.

Sample Size Calculation: From previous study: Echocardiographic evaluation of heart in COPD patients and its co - relation with the severity of disease On echocardiographic evaluation of COPD 50% cases ha abnormal echocardiographic parameters. So, P=0.50, 1.96= z value for 5% confidence level, e= Allowable error =10% Cochran formula for observational study

Minimum Sample Size=N = 1.962
$*p*$ $(1-p)$ 2 = 1.962
$*P*$ $(1 - P)$ /e2= (3.8416*0.50*0.50) / (0.10) 2=97
100 patients were taken.

Randomization by computer generated random numbers

Method of Collection of Data

Hundred patients of COPD confirmed by clinical history, radiology of chest, and pulmonary function test (COSM Pulmonary function equipment) are selected from General medicine department of Ramakrishna care hospital Raipur, Chhattisgarh. Patients are selected as per inclusion and exclusion criteria as described.

All the patients were investigated by spirometry and diagnosed and classified according to GOLD guidelines (post bronchodilator FEV 1 /forced vital capacity (FVC) ratio < 70% predicted), mild (FEV 1 ≥ 80% of predicted), moderate (50% ≤ FEV 1 < 80% predicted), severe (30% ≤ FEV 1 < 50% predicted), and very severe (FEV 1 < 30% predicted), All patients are subjected to resting Two - dimension transthoracic Doppler echocardiography by expert cardiologists. The machine used is EPIQ 7 PHILLIIPS model.

Pulmonary hypertension (PH) is defined in this study as sPAP ≥ 30 mmHg. [38]This value was chosen according to the definition of pulmonary hypertension. PH is classified into mild, moderate, and severe category as sPAP 30 - 50, 50 - 70, >70 mmHg, respectively (using Chemla formula, mean pulmonary arterial pressure (MPAP) =0.61 PASP + 2 mmHg and putting value of 25 - 35, 35 - 45, and>45 mmHg of MPAP for mild, moderate, and severe pulmonary hypertension, respectively). [19]

Right ventricle dimension were measured by M - Mode echo and right ventricular dilation or cor pulmonale was said to be present when it exceeded the normal range of 0.9 - 2.6 cm. E/A = diastolic filling of left ventricles usually classified initially on the basis of the peak mitral flow velocity of the early rapid filling wave (E), peak velocity of the late filling wave caused by atrial contraction (A). In normal subjects LV elastic recoil is vigorous because of normal myocardial

relaxation, therefore more filling is completed during early diastolic, so left ventricular diastolic dysfunction (LVDD) is said to be present when E/A is <1.3 (age group 45 - 49 years), <1.2 (age group 50 - 59 years), <1.0 (age group 60 - 69 years), and <0.8 (age group ≥70 years). [20]

Chest X ray:
SIEMENS Multiphos 15 respectively (Spirometry - Care fusion - MS Diff).

Statistical Methods:
The statistical analysis was done using SPSS (Statistical packages for Social Sciences) Version 16.0 software. The following Statistical formulas were used:

1) Mean: Individual observations are summed and then divided by the number of observations, mean is obtained. Where X stands for mean Signifies sum of individual observations X indicates individual observations n denotes number of observations

2) Chi square test (to find the significance of association between varibles such as BMI, Comorbidity according to severity of COPD):

Chi square value $=\sum O - E$ 2E O is observed frequency E is expected frequency
Degree of freedom= (Row - 1) (column - 1)

ANOVA (for comparing mean duration of COPD according to severity of COPD): Study design: Prospective observational study

Statistical analysis was performed by the SPSS program for Windows, version 20.0. Continuous variables were presented as mean ± SD, and categorical variables were presented as absolute numbers and percentage. Data checked for normality before statistical analysis. Normally distributed continuous variables compared using the ANOVA for significant difference in mean, whereas the Mann - Whitney U test was used for those variables that will not be normally distributed. Categorical variables were analyzed using either the chi square test or Fisher's exact test. For all statistical tests statistical significance were decided as given below

P>0.05 is not significant
P<0.05 is significant
P<0.01 Highly significant
Software used: SPSS 20.0

4. Observation and Results

Age wise Distribution in COPD patients: The maximum number of COPD patients in this study was in the age group of 61 to 70 yeas (39%) followed by 51 to 60 years (30%).

Sex wise Distribution in COPD patients: In our study higher incidence of COPD found in males (86%) compared to females (14%).

BMI correlation with COPD severity:
In our study the Normal BMI was found in 58% COPD patients followed by low BMI in 31% COPD patients. In our study normal BMI was commonly found in moderate and severe COPD patients and low BMI found in very severe

COPD patients, **So BMI is significantly associated with severity of COPD (P value <0.0001).**

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Symptoms in COPD patients:

Clinical findings	N (%)
Cough with sputum	86
Dyspnoea	96
Swelling feet	36
Fever	16

Our study shows most common symptoms are cough with sputum (86%) and breathlessness on presentation (96%).36% presented with swelling of feet, 16% has fever.

Duration of COPD symptoms: In our study mean duration of symptoms in Mild COPD is 3.5+ 1.29 years, 8.09+2.63 in moderate copd patients, 10.79+ 3.69 years in severe COPD patients and 16.2 + 3.78 years in very severe COPD patients. **Mean Duration of COPD is significantly associated with severity of COPD** (P <0.0001).

Pack years of smoking in COPD:

our study shows mean pack years of smoking in mild COPD is 10.5+5.68, moderate is 15.23+9.14, severe COPD is 24.94 + 5.82 and in very severe COPD is 36.52+6.99 years.

Pack years of smoking is highly significantly associated with severity of COPD (Pvalue<0.0001).

Severity of the COPD (GOLD Classification):
In our study majority of patients (49%) had severe and very severe COPD (25%), 22% had moderate COPD and 4% patients had mild COPD.

Symptoms and signs wise distribution in COPD patients: In our study most of the patients had cough with sputum (86%) and breathlessness on presentation (96%).36% presented with swelling of feet, 16% had fever.

Most common sign at presentation is tachypnea in 95% followed by 44% had loud P2 suggestive of pulmonary arterial hypertension, 36% of the patients had parasternal heave, the clinical signs of right ventricular hypertrophy. Evidence of congestive cardiac failure like raised JVP in 31%, pedal edema in 35% and ascites in 13% cases.8% of the patients had cyanosis which is evidence of a hypoxic state.

Comorbidities correlation with COPD severity:
In our study most common comrbidities are Hypertension (40%), CCF (30%) and DM (24%). Comorbidities are more common in severe and very severe COPD. comorbidities are not significantly associated with severity of COPD (P Value 0.47).

Chest X ray findings in COPD:
In chest X - ray, 73% of the patients had features of emphysema.44% of the patients had increased brochovascular marking. X - ray evidence of pulmonary hypertension i. e. prominent right descending pulmonary artery (RDPA) was present in 32% of the patients.

Cardiomegaly on X - ray found in 24%. Emphysematous chest x ray changes are commonly seen in severe COPD (63.01%), cardiomegaly and Prominent RDPA>16mm changes are commonly seen in very severe COPD, 62.5% and 50% respectively. Emphysematous changes, increased BVM, Cardiomegaly changes and Prominent RDPA>16mm in chest x ray are significantly associated with severity of COPD.

Correlation of Echocardiographic findings with severity of COPD:
In the present study, the incidence of all the echocardiographic findings increased as the severity of the disease increased, i. e. maximum incidence was found in the most severely affected group of patients.
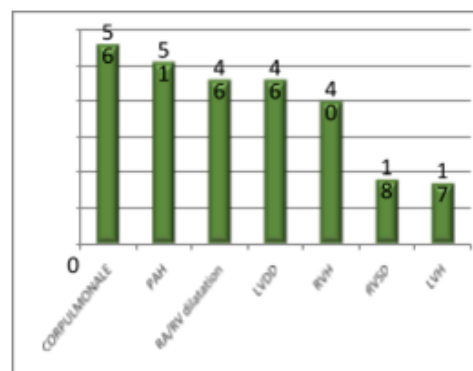
In our study most common chocardiographic findings are Cor - pulmonale (56%), followed by PAH (51%), Followed by RA/RV dilatation and LVDD (46% each), followed by RVH (40%), LVH (17%), RVSD (18%).

In our study RA/RV dilatation mainly found in severe and very severe COPD (43.48% in each), its significantly associated with severity of COPD (P value 0.0003).

In our study Cor - pulmonale is most common finding in echocardiography (56%), in which 55.36% found in severe COPD and 35.71% found in very severe COPD. Its significantly associated with severity of COPD (P value 0.0016). In our study PAH found in 51% of COPD patients, 17.65% in moderate COPD, 45.1% insevere COPD patients and 37.25% in very severe COPD. PAH is highly significant with severity of COPD (P Value 0.009). In present study RVH seen in 10% of moderate COPD, 47.5% in severe COPD and 42.5% in very severe COPD patients. RVH is significantly associated with severity of COPD (P value0.0016).

In our study LVH found in 17% of COPD patients, 35.29% in severe COPD patients and 52.94% in very severe COPD. LVH is significantly associated with severity of COPD (PValue 0.02).

In our study RVSD found in 18% COPD patients. Its not significantly associated with severity of COPD (P value 0.3). The higher incidence of cor - pulmonale in the studies can be explained by the fact that all patients in that study had severe airway obstruction.

In our study LVDD found in 46% of COPD patients, 17.39% in moderate COPD, 50% in severe COPD patients and 32.61% in very severe COPD. LVH has no significant association with severity of COPD.

5. Summary

The maximum number of COPD patients in this study was in the age group of 61 to70 yeas (39%) followed by 51 to 60 years (30%).
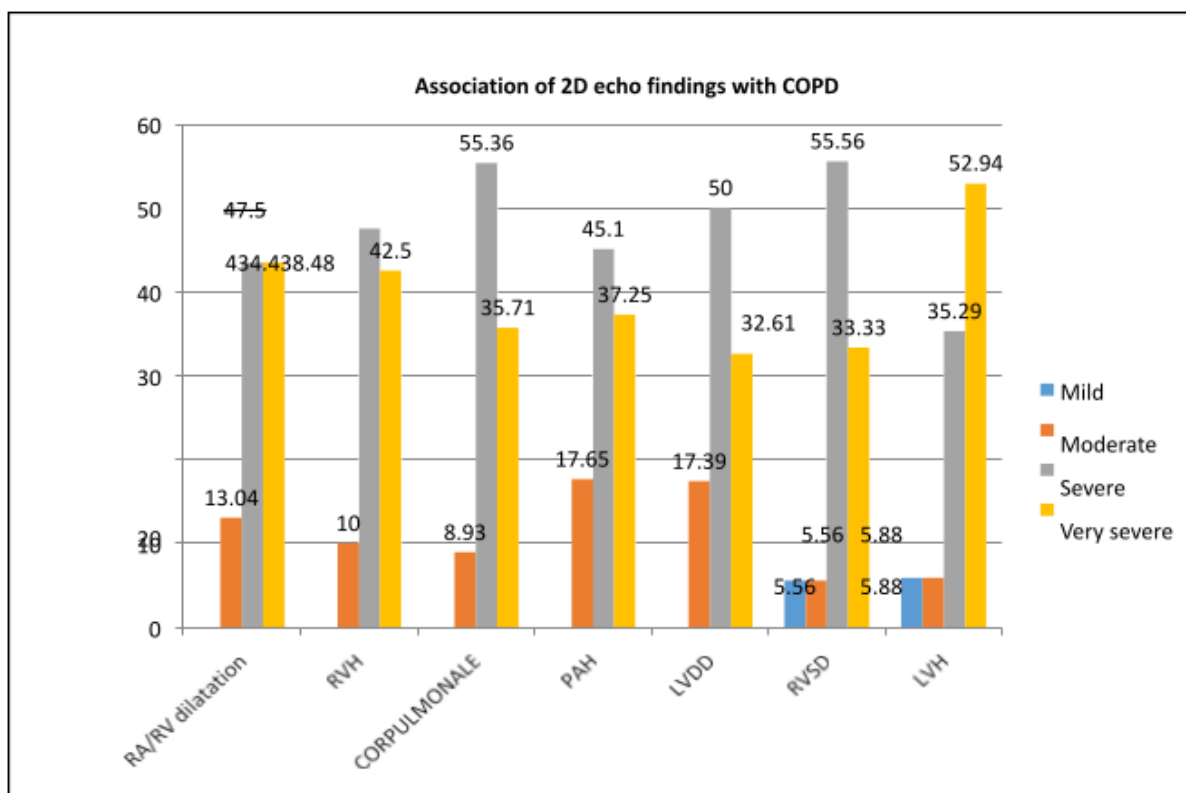
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Pack years of smoking in mild COPD is 10.5+5.68, moderate is 15.23+9.14, severe COPD is 24.94 + 5.82 and in very severe COPD is 36.52+6.99 years. Pack years of smoking is highly significantly associated with severity of COPD (P value<0.0001).

Majority of patients has severe COPD (49%) and very severe COPD (25%), followed by 22% has moderate COPD and 4% patients has mild COPD.

Most common symptoms are cough with sputum (86%) and breathlessness on presentation (96%).36% presented with swelling of feet, 16% had fever.

Most common sign at presentation is tachypnea in 95% followed by 44% had loud P2 suggestive of pulmonary arterial hypertension, 36% of the patients had parasternal heave, the clinical signs of right ventricular hypertrophy. Evidence of congestive cardiac failure like raised JVP in 31%, pedal edema in 35% and ascites in 13% cases.8% of the patients had cyanosis which is evidence of a hypoxic state.

Normal BMI was found in 58% COPD patients followed by low BMI in 31% COPD patients. In our study normal BMI was commonly found in moderate and severe COPD patients and low BMI found in very severe COPD patients, So BMI is significantly associated with severity of COPD (P value <0.0001).

Most common comrbidities are Hypertension (40%), CCF (30%) and DM (24%). comorbidities are more common in severe and very severe COPD. Comorbidities arenot significantly associated with severity of COPD (P Value 0.47).

In chest X - ray, 73% of the patients had features of emphysema.44% of the patients had increased brochovascular marking. X - ray evidence of pulmonary hypertension i. e. prominent right descending pulmonary artery (RDPA) was present in 32% of thepatients. Cardiomegaly on X - ray found in 24%. Emphysematous chest x ray changes are commonly seen in severe COPD (63.01%), cardiomegaly and Prominent RDPA>16mm changes are commonly seen in very severe COPD, 62.5%

and 50% respectively. Emphysematous changes, increased BVM, cardiomegaly changes and Prominent RDPA>16mm in chest x ray are significantly associated with severity of COPD.

In our study most common Ehocardiographic findings are Cor - pulmonale (56%), followed by PAH (51%), Followed by RA/RV dilatation and LVDD (46% each), RA/RV dilatation mainly found in severe and very severe COPD (43.48% in each), its significantly associated with severity of COPD (P value 0.0003).

Cor- pulmonale is most common finding in echocardiography (56%), in which 55.36%found in severe COPD and 35.71% found in very severe COPD. Its significantly associated with severity of COPD (P value 0.0016). PAH found in 51% of COPD patients, 17.65% in moderate COPD, 45.1% in severe COPD patients and 37.25% in very severe COPD. PAH is highly significant with severity of COPD (P Value 0.009). RVH seen in 10% of moderate COPD, 47.5% in severe COPD and 42.5% in very severe COPD patients. RVH is significantly associated with severity of COPD (Pvalue 0.0016).

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RVSD found in 18% COPD patients. Its not significantly associated with severity of COPD (P value 0.3).

6. Conclusion

Echocardiographic evidence of cor - pulmonale was found in 56% of patients, pulmonary hypertension in 51%. Statistically significant correlation with severity was found in the incidence of RA and RV dilatation, PAH, Cor - pulmonale and LVH among echo finding (P value < 0.05). The severity of complications increases with severity of COPD and makes a linear relation.2D echocardiography is more sensitive than radiography and clinical methods in detecting cardiovascular complications like PAH, cor pulmonale and RV. Dysfunction in COPD patients.

Echocardiography provides a rapid, non - invasive, portable, and accurate method to evaluate cardiac functions in COPD patients.

Smoking cessation is the effective intervention in stopping the progression of COPD, as well as increasing survival and reducing morbidity. This is why smoking cessation should be the top priority in the treatment of COPD.

Our study is a prospective observational study where one hundred COPD patients were taken and the high prevalence of cardiac comorbidities such as PAH, Cor - pulmonale, RV Early diagnosis and intervention for cardiac comorbidities would reduce mortalities45

7. Recommendations

It is recommended that Echocardiography should be done early in all cases of COPD to diagnose the cardiac complications of COPD, so that early interventions can be undertaken in order to improve quality of life and decrease mortality and morbidity in COPD patients.

An optimal approach to smoking cessation today should contain an adequate support programme, either individual or in groups, in combination with a first - line pharmacological smoking cessation agent, i. e. NRT (two formulations), varenicline orbupropion SR for 3 months. When relapse occurs, re - treatment should be offered. COPD patients need more support than smokers without comorbidities and smoking intervention should have top priority as it is very cost - effective, reduces the decline in lung function and reduces morbidity and mortality.

Our study findings support the obesity paradox in COPD: compared to normal BMI, Low BMI is a risk factor for accelerated lung function decline, whilst high BMI has a protective effect. COPD patients categorized by BMI groups differ in survival and cause of death, also showing that patients with COPD manifest different physiological, functional and perceptive expressions according to their BMI. Taken together, these results support the use of BMI as a stratifying variable to grade COPD which may reveal novel endotypes or targets for therapeutic intervention in nutritional part in COPD.

8. Limitations of Study

In our study we mostly included admitted patients because all data collection which needed found easily and opd patients who's complete data is available were included in study. In our study we taken smoking as risk factor for COPD, other risk factors like Genetic, occupational etc were not taken.

References

[1] Silverman RJ. Chronic obstructive pulmonary disease. In: Kasper D. Harrisons manual of medicine. Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. McGraw - Hill Medical Publishing Division.2015; 2: 1700.
[2] Daniels LB, Krummen DE, Blanchard DG. Echocardiography in pulmonary vascular disease. Cardiol Clin.2004; 22: 383 - 99.
[3] Murray CJ, Lopez AD. Evidence based health policy - lessons from the Global Burden of disease Study. Science.1996; 274: 740 - 3.
[4] World Health Report. Geneva: World Health Organisation.2000.
[5] National Heart, Lung, and Blood Institute. COPD essentials for health professionals. NIH Publication No.07 - 5845.
[6] Stoller JK, Fromer L, Brantly M, et al. Primary care diagnosis of alpha - 1 antitrypsin deficiency: issues and opportunities. Cleve Clin J Med.2007; 74: 869 - 874
[7] Sutherland ER, Cherniack RM. Management of chronic obstructive pulmonary disease. N Engl J Med.2004; 350: 2689 - 2697
[8] Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research

Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax.1999; 54: 581 - 6.

[9] Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J.2009; 34: 648 - 54.

[10] Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5 - year mortality: A randomized clinical trial. Ann Intern Med.2005; 142: 233 - 9.

[11] Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation.1984; 70: 657 - 62.

[12] Tramarin R, Torbicki A, Marchandise B, Laaban JP, Morpurgo M. Doppler echocardiographic evaluation of pulmonary artery pressure in chronic obstructive pulmonary disease. A European multicentre study. Eur Heart J.1991; 12: 103 - 11.

[13] Weitzenblum E, Chaouat A. Cor pulmonale. Chron Respir Dis.2009; 6: 177 - 85.

[14] Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA.2002; 288: 2144 - 50.

[15] Rodeheffer R, Miller W, Burnett J. Pathophysiology of circulatory failure. In: Giuliani E, Gersh B, Megoon M, Hayes D, Schaff H, editors. Mayo Clinic Practice of Clinical Cardiology.3rd ed. Mosby; 1996. pp.556 - 8.

[16] Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: An epidemiologic perspective J Am Coll Cardiol.1995; 26: 1565 - 74.

[17] Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M, et al. Left atrial

[18] and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. Am J Respir Crit Care Med.2000; 162 (2 Pt1): 670 - 5.

[19] Bhattacharyya P, Roy Chowdhury S, Nag S, Sarkar D, Ghosh G, Bardhan S, et al. Diastolic dysfunction in advanced COPD patients: Early results of an observational study. Respirology.2004; 9: A98.

[20] Chemla D, Castelain V, Humbert M, Simonneau JLHG, Lecarpentier Y, Hervé P. New Formula for Predicting Mean Pulmonary Artery Pressure Using Systolic Pulmonary Artery Pressure. Chest.2004; 126: 1313 - 17.

[21] Libby P, Bonow RO, Zipes DP, Mann DL, editors.8 th. Philadelphia: Saunders; 2008. Braunwald's Heart Disease; p.251.