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Original Research Article

Evaluation of Ischemic Heart Disease in Patients of Chronic Obstructive Pulmonary Disease in aTertiary Care Hospital

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Abstract

Introduction: Patients with COPD are at increased risk of an array of acute cardiovascular events, including myocardial infarction and have increased short-term and long-term mortality compared with their non-COPD counterparts. In fact, up to one-third of deaths in patients with COPD may be described to cardiovascular disease. Hence the study is taken up to evaluate the prevalence of IHD in patients of COPD in a tertiary care hospital.

Methodology: A cross sectional study was conducted in the Dept. of General Medicine and Respiratory Medicine of AGMC & GBP Hospital from January 2016 to July 2017 among 135 COPD patients who were selected consecutively. Data were collected in a case record form and analysed using Microsoft excel.

Result: The mean age of the participants was 65 ± 7 years ranges from 50 to 85 years where male was more (93.3%). Among 135 participants, 84 (64%) were current smoker and 65% of them were of stage II & III COPD gold stage. Only 28% of echocardiography shown regional wall motion abnormalities (RWMA) suggestive of Ischemic heart disease (IHD) out of all COPD patients. Advance age, smoker and reactive to CRP were strongly associated with presence of IHD.

Conclusion: One third of COPD patients are having ischemic heart diseases. Advance age, smoker, and reactive to CRP were strongly associated with presence of IHD among COPD patients. Hence, screening for cardiovascular diseases is recommended among COPD patients in hospitals.

Keyword: Ischemic heart disease, COPD, CVD evaluation, Echocardiography

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by airflow limitation that is not fully reversible. COPD includes emphysema, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and small airways disease, a condition in which small airways are narrowed. COPD is present only if chronic airflow obstruction occurs; chronic bronchitis without chronic airflow obstruction is not included within COPD.[1] India also contributes a significant and growing percentage of COPD mortality estimated to be amongst the highest in the world; i.e. more than 64.7 estimated age standardized death rate per 100,000 amongst both sexes as mentioned in the WHO Global InfoBase Updated on 20th January 2011.[2]

There are many risk factors for COPD. Cigarette smoking is the principal cause of COPD but the relationship is complex and COPD may develop without a smoking history. Workers exposed to dust in certain workplace environments may suffer permanent loss of lung function. Current urban air pollution in economically advanced countries appears to have little effect on the prevalence of airflow obstruction but this factor may be more important in heavily polluted urban centres in industrializing countries. Recurrent respiratory infections were once thought to be a major factor in the development of airflow obstruction but longitudinal cohort studies have yielded inconclusive findings. A severe deficiency of α1- antitrypsin is the only genetic risk factor proven to have a major impact on the development of COPD. This deficiency is found in about 1 to 2% of patients with an established diagnosis of COPD. [3]

The cardiovascular sequelae of COPD have been recognized for decades. The spectrum of CVD includes right ventricular dysfunction, pulmonary hypertension, coronary artery disease and arrhythmias.[4] The Lung Health Study showed that a substantial proportion of deaths in patients with mild COPD were the result of cardiovascular complication and a large epidemiologic study revealed increased cardiovascular mortality, particularly in patients younger than 65 years with COPD. [5,6] Patients with COPD are at an increased risk of an array of acute cardiovascular events, including myocardial infarction (MI) and have increased short-term and long-term mortality compared with their non-COPD counterparts. In fact, up to one-third of deaths in patients with COPD may be ascribed to cardiovascular disease. Cardiovascular mortality increases by 28% for every 10% decrement in forced expiratory volume in 1 s (FEV_1). Finally, the presence of COPD is associated with worse long-term outcome in patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass graft.[7] Various studies have reported a strong link between the occurrence of COPD and the presence of CAD. The causal link between these diseases has historically been cigarette smoking but the exact mechanisms have only recently been studied. [8]

Epidemiologic evidence supports the importance of systemic inflammation in the pathogenesis of atheroma formation and ischemic heart disease and recent studies have indicated that patients with COPD have a prominent systemic inflammatory response. C-reactive protein (CRP), a known marker of systemic inflammation [9], for example, has been shown to be elevated in patients with both stable COPD and during exacerbation.

Because elevations in CRP have been linked to CAD[10], it appears as though the pathogenesis of both COPD and CAD may stem from enhanced systemic inflammation. A study has suggested that cell senescence (shortened telomere length as a surrogate biomarker) is found in patients with ischemic heart disease (IHD) and similarly, early senescence may contribute to the development of emphysema. Lung inflammation is an intrinsic component in the pathogenesis of COPD leading to systemic inflammation which contributes to atherosclerosis and IHD. [11]

COPD-related systemic inflammatory status may also significantly affect platelet reactivity and responsiveness to antiplatelet drugs. Indeed, as a result of inflammation, COPD patients have decreased platelet volume and increased platelet count.[12] COPD is strongly related to increased arterial stiffness because of several factors: increased blood pressure (systolic and diastolic), severity of inflammation, increased coronary artery calcium, older age, imbalance between proteases and anti-proteases, severity of hypoxia and chronic hyperglycemia.

The relationship between various inflammatory markers and coronary artery disease (CAD) has been established long ago. Among them, WBC subtypes have emerged as a community of inflammatory markers playing a crucial role in the pathogenesis of a thermogenesis and atherothrombosis. Neutrophil-to-lymphocyte ratio (NLR), a new addition to the long list of markers- is an inexpensive, easy to obtain, widely available marker of inflammation which can aid in the risk stratification of patients with various cardiovascular diseases in addition to the traditionally used markers. The main role of neutrophilia in CAD may be explained by secretion of various inflammatory mediators such as elastase, myeloperoxidase and oxygen free radicals which causes tissue damage. The probable cause of lymphopenia include decreased production as a result of increased steroid level due to CAD induced stress and increased apoptosis triggered by increased inflammation thereby resulting in elevated NLR in CAD. [13]

Platelet-to-lymphocyte ratio (PLR) is a new prognostic index that gives an about both the aggregation and inflammation pathways. Increased PLR values emerged as a valuable predictor of adverse cardiovascular events in certain types of acute coronary syndromes in the long term and in predicting critical limb ischemia in peripheral artery disease. Moreover, higher PLR values emerged as a significant index that may independently predict the severity of coronary atherosclerotic disease. [14]

In view of the increased cardiovascular mortality, it is important to increase awareness in the community regarding IHD in COPD. In addition to smoking cessation programs, early screening of all patients diagnosed with COPD should be done to identify cardiovascular complications and initiate early therapy. Hence, this study is taken up to evaluate the prevalence of IHD in patients of COPD in a tertiary care hospital.

Methodology

A cross sectional study was conducted in the Department of Medicine, AGMC & GBP Hospital in collaboration with Dept. of Chest Medicine for a period from January 2016 to July 2017 among the patients diagnosed with COPD. Total sample size calculated was 135 who were selected conveniently. Those who are attended in OPD or admitted in the ward and diagnosed as chronic obstructive pulmonary disease (COPD) based on spirometric assessment are included in the study. Participants having reversible airway obstruction on spirometry (Bronchial asthma), Diabetes mellitus, Hypertension, Dyslipidemia, Chronic kidney disease (CKD), Active infection, Known systemic inflammatory condition or autoimmune

disease, any Malignancy, Chronic liver disease (CLD) and Patient using steroids were excluded from the study.

Subjects were diagnosed as COPD on the basis of History (cough, sputum production and exertional dyspnea of long duration, smoking history, occupational history, family and personal history, exposure to environmental tobacco smoke, education and marital status). Clinical examination and Spirometry was performed in the OPD of Department of Respiratory Medicine. COPD was diagnosed by GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria: [15] The spirometric criterion for COPD is presence of post bronchodilator ratio of FEV_1/FVC <0.70. Possible dosage protocols are 400µg $beta_2$-agonist, 160µg anticholinergic, or the two combined. FEV1 should be measured 10-15 minutes after a short acting beta2-agonist is given or 30-45 minutes after a short-acting anticholinergic or a combination. Spirometric measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex and race.

All patients underwent baseline investigations like blood pressure measurement, height and weight measurement fasting and post prandial blood glucose, lipid profile, blood urea nitrogen (BUN), serum creatinine and complete blood count (CBC) and C reactive protein (CRP) level. Patients not fulfilling the selection criteria were excluded. After obtaining written informed consent, a 12 lead electrocardiography (ECG) was performed on each patient and abnormalities suggestive of IHD were recorded. Although any abnormality can be a manifestation of IHD, we have selected the following abnormalities in our study.

Electrocardiographic changes suggestive of IHD: [16] ST segment elevation >0.1mV in limb leads and/or >0.2mV in precordial leads suggestive of myocardial infarction. ST segment depression of >0.05mV in at least two contiguous leads. Increased hyperacute T waves with prominent symmetric T waves in two contiguous leads. Symmetric T wave inversion of >0.01mV in at least two contiguous leads. Pathologic Q waves. A transthoracic echocardiography was performed on all patients and regional wall motion abnormalities (RWMA) were looked for suggestive of IHD. [17] From the CBC report, total leucocyte count (TLC), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) was calculated for every individual. A cut-off value of 2.1 for NLR has been used in our study for presence of coronary artery disease (CAD) and a cut-off value of 132 for PLR has been used for presence of CAD in COPD patients. [18]

Data were collected in case record form. Data were expressed in terms of percentages or proportions and appropriate tables and charts are used as and where required. Data were assessed and analyzed by statistical software SPSS version 15.0. Pearson Chi square test, Fisher exact test, binary logistic regression method and linear regression method were used wherever applicable. A P value of ≤0.05 was considered statistically significant. A ethical approval also taken prior to the data collection.

Result

This cross sectional study was carried out in the ward and OPD of the department of General Medicine at Agartala Government Medical College & GB Pant Hospital between January 2016 and July 2017. Following strict inclusion and exclusion criteria as mentioned before, we obtained a total of one hundred and thirty five (135) cases for this study. The following were the observations and deductions made out of subsequent analysis of the data obtained from the study of 135 patients who were suffering from Chronic Obstructive Pulmonary Disease (COPD) who met the inclusion criteria admitted in the ward or visiting OPD of the department of General Medicine at AGMC & GBP Hospital. The

mean age of the participants was 65 ± 7 years ranges from 50 to 85 years where male were more (93.3%). 126 (93.3%) out of 135 COPD patients are male. Aged 60-70 years old were majority (64.4%). Out of 135 patients, more than half of them i.e. 53.3% were unemployed while among the employed ones, labourer (27.4%) and farmer (12.6%) were the major occupations. Among the 135 cases, 52.6% people had completed primary education while 29.6% had completed upper primary education and 17.8% were illiterate. Among the 135 cases, 67.4% were non-tribal whereas 32.6% belonged to the tribal community. Out of the 135 cases, majority of them i.e. 93.3% were married while 3.0% were widows and 3.7% were widowers. Body Mass Index (BMI) was calculated in kg/m^2. 71.9% individuals were found to have normal BMI while 205 were underweight and 8.1% were overweight. Out of the 135 cases, 62.2% were current smokers while 25.9% were former smokers and 11.9% were non-smokers. (Table 1)

Table 1: Smoking status (N=135)

Smoking status	Frequency	Percentage
Current	84	62.2
Former	35	25.9
Non-smoker	16	11.9
Total	135	100.0

Among the 135 cases, 119 were smokers. Out of the 119 smokers, 32 had a smoking index of 300-350, 62 had an index of 350-400 and 25 had an index of 400-450. (Table 2)

Table 2: Smoking Index

Smoking index	Frequency	Percentage
300-350	32	23.7
350-400	62	45.9
400-450	25	18.5
Nil	16	11.9
Total	135	100.0

Among the 135 patients, 25.2% had COPD stage I, 32.6% were in stage II, 31.1% were in stage III and 11.1% were in stage IV. (Table 3)

Table 3: COPD GOLD staging (N=135)

GOLD staging	Frequency	Percentage
I	34	25.2
II	44	32.6
III	42	31.1
IV	15	11.1
Total	135	100.0

Table 4: ECG abnormalities (N=135)

ECG	Frequency	Percentage
Atrial fibrillation	5	3.7
Bifascicular block	1	0.7
LBBB	7	5.2
LVH	14	10.4
MAT	2	1.5

Q wave	9	6.7
RBBB	9	6.7
Sinus tachycardia	6	4.4
ST depression	22	16.3
T inversion	5	3.7
WNL	55	40.7
Total	135	100.0

Among the 135 ECGs, 40.7% were normal while the remaining ECGs showed various abnormalities as depicted above.

Out of the 135 patients, 28.1% patients showed regional wall motion abnormalities (RWMA) suggestive of IHD while the remaining had a normal echocardiography or findings not specific for IHD. Out of the 135 subjects, 48.1% had a positive CRP while the remaining 51.95% had a normal CRP value. Out of the 135 cases, IHD was present in 28.1% of cases and 71.9% cases did not have IHD.

Using the linear regression analysis as shown in table 5, calculated p value was 0.028 (<0.05) which is statistically significant. This shows that there is a significant association with age of the patient and prevalence of ischemic heart disease in this study.

Table 5: Association of Age with IHD (N=135)

Variable	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta	B	Std. Error
(Constant)	0.926	0.358		2.583	0.011
Age	0.012	0.005	0.189	2.226	0.028

Table 6: Association between smoking status and IHD (N=135)

Smoking status	B	S.E.	Wald	df	Sig.	Exp(B)
Current			1.860	2	0.039	
Former	-0.351	0.623	0.318	1	0.057	0.704
Non smoker	0.288	0.715	0.162	1	0.688	1.333
Constant	1.099	0.577	3.621	1	0.57	3.000

Binary logistic regression method was applied and p value was found to be 0.039, 0.057 and 0.688 for current smokers, former smokers and non-smokers respectively. Current smoker is found to be statistically significant and associated with the prevalence of IHD in this study.

To find the association between different GOLD stages of COPD, binary logistic regression was applied. It shows a p value of <0.001 for Stages I, II and III whereas p value for Stage IV is 0.006 (<0.05) which is statistically significant. This shows that COPD stages have a significant association with prevalence of IHD in this study. (Table 7).

Table 7: Shows association between COPD Gold staging and IHD (N=135)

GOLD staging	B	S.E.	Wald	Df	Sig.	Exp(B)
I			20.256	3	.000	
II	4.883	1.203	16.477	1	.000	132.000
III	2.610	.739	12.475	1	.000	13.600
IV	1.974	.721	7.489	1	.006	7.200
Constant	-1.386	.645	4.612	1	.032	.250

C reactive protein was higher (55.3%) in ischemic heart disease. Using the Pearson Chi square test, p value was found to be 0.000 which is statistically significant. Thus there is a strong association between high CRP value and prevalence of IHD in this study. (Table 8)

Table 8: Association of CRP with IHD

C-Reactive protein	Ischemic heart disease		P value
	Present	Absent	
Negative	2 (2.85)	68 (97.15)	0.000
Positive	36 (55.3)	29 (44.7)	
Total	38	97	

Discussion

Observations made in the 135 cases of COPD after investigations are discussed here and compared with similar studies.

The prevalence of Ischemic heart disease (IHD) in COPD patients in this study was found to be 28.1%. This is similar to the results obtained in the study conducted by Mapel DW et al (33.6%), Hua Cui et al (28.9%) and Michela Bellocchia et al (25%).

After comparing the baseline characteristics of patients with prevalence of IHD it was found that age of the patient was significantly associated with IHD ($p<0.05$). Majority of the patients (64.4%) were in the age group of 60-70 years. Thus the prevalence of IHD increases with increasing age in a COPD patient.

Out of the 135 cases, 93.3% were males and 6.75 were females. However, sex of the patient had no statistically significant association with the prevalence of IHD in this study. The patient population belonged to variety of occupations; 53.3% being unemployed and the remaining worked as farmers, laborers, drivers and shopkeepers.

This study was conducted in the state of Tripura where tribal as well as nontribal communities reside. Of the 91 nontribal patients, IHD was present in 26 cases and among the 44 tribal patients IHD was present in 12 cases. However, the association was not statistically significant($p>0.05$).

Education status of the patients was also taken into consideration. 52.6% patients were educated up to the primary level while others were either illiterate or had completed upper primary education.

The educational level of the patient had no significant association with the prevalence of IHD. Out of the 135 cases, 93.3% were married. However, the marital status of the individual was not significantly associated with IHD.

Smoking status of the individuals was also recorded and classified as current smokers (smoked >100 cigarettes in lifetime and currently smoking), former smokers (smoked>100 cigarettes in lifetime but quit smoking) and non-smokers (never smoked or smoked <100 cigarettes in lifetime). 62.2% of cases were current smokers. However, on analysis it was found that the smoking status had no significant association with prevalence of IHD in COPD. This emphasizes the fact that COPD as well as IHD have multiple risk factors including environmental and genetic factors and can occur in non-smokers too.

Similar to the smoking status, smoking index was also calculated as the number of cigarettes/bidis smoked per day multiplied by the number of years smoked. Out of the 119 smokers, 62 had a smoking index of 350-400. However, on applying statistical tests, no significant association was found with the prevalence of IHD. Thus, though smoking index may be associated with increased prevalence of COPD or other respiratory diseases, it had no association with prevalence of IHD in this study.

COPD staging was done for all patients as per the GOLD criteria. Most of the cases belonged to Stage II and III. It was found that all COPD stages had a strong significant association ($p<0.001$) with the prevalence of IHD in this study. At the time of this study, many patients enrolled were already on treatment for COPD (57.8%). However, treatment of COPD had no statistically significant relationship with the prevalence of IHD.

After taking into consideration the baseline characteristics, 12 lead ECG was performed on all cases to look for signs of ischemic heart disease. Among all the findings, flat or down sloping ST segment depression >0.1mV below baseline, symmetric T wave inversion and pathologic Q waves were taken as indicators of IHD. Accordingly, 40.7% cases had normal ECG whereas 26.7% individuals had findings suggestive of IHD on ECG. Thus, ECG findings for IHD were positive in 26.7% of cases among the total 28.1% of IHD cases in this study.

Transthoracic echocardiography was performed on all individuals and regional wall motion abnormalities (RWMA) was selected as the indicator of IHD. Out of the 135 cases, 38 cases (28.1%) had RWMA while the rest had normal echocardiography or findings not suggestive of IHD.

CRP (C reactive protein) was estimated as a marker of systemic inflammation in all cases as COPD and IHD are linked by systemic inflammatory state. 65 cases had a positive CRP value out of which 36 were found to have IHD. This was found to be statistically significant ($p<0.001$) after applying Pearson Chi square test. The sensitivity of CRP in detecting presence of IHD was found to be 94.7% and specificity was found to be 70.1%.

Total leucocyte count (TLC) was measured of all subjects and equated with the prevalence of IHD as well as the abnormalities found on echocardiography. The mean TLC in this study was 8376 cells/mm3. Statistical tests showed that TLC was significantly associated ($p<0.001$) with prevalence of IHD in COPD patients. On comparing with echocardiographic findings, it was found that patients with higher TLC values were more likely to have RWMA in their echocardiography while those with lower TLC values were likely to have a normal echocardiography. However, there was no clear demarcation between the two and a cut-off value could not be selected. Thus, higher TLC values indicate systemic inflammation and occurrence of ischemic heart disease in COPD.

Neutrophil to lymphocyte ratio (NLR) was calculated in all subjects from the complete blood count (CBC). The NLR values ranged from 1.1 to 3.2 with a mean value of 1.7. A cut-off value of 2.1 was selected to predict the presence of coronary artery disease in COPD patients. This cut-off value was selected in accordance with the study performed by Sharma et al in Western Indian population. In this study, it was found that among the 38 IHD patients, NLR was more than 2.1 in 29 cases. This was statistically significant ($p<0.001$) and thus NLR can be used as a novel biomarker of IHD in COPD patients. On correlating NLR values with echocardiographic findings, individuals with higher NLR values were more likely to have RWMA in echocardiography. The sensitivity and specificity of NLR in detection of IHD in COPD in this study was 76.3% and 94.8% respectively. The study conducted by Sharma et al on the basis of which the cut-off value was taken had a sensitivity of 83.64% and specificity of 63.46% for NLR in detecting CAD. This disparity could be due to larger sample size (n=324) and presence of other comorbidities like hypertension and diabetes mellitus. Platelet to lymphocyte ratio (PLR) was also calculated in all subjects. The PLR values ranged from 111 to 190 with a mean value of 143. A cut-off value of 132 was selected to predict the presence of coronary artery disease in COPD patients. This cut-off value was selected in accordance with the study performed by U çar et al. In this

study, it was found that among the 38 IHD patients, PLR was more than 132 in 36 cases. This was statistically significant ($p<0.001$) and thus PLR can also be used as a novel biomarker of IHD in COPD patients. On correlating PLR values with echocardiographic findings, individuals with higher PLR values were more likely to have RWMA in echocardiography. The sensitivity and specificity of PLR in detection of IHD in COPD in this study was 94.7% and 56.7% respectively. The similar study conducted by U car et al showed a sensitivity of 76% and specificity of 60% for the same cut-off value. This disparity is probably due to inclusion of confounding factors like hypertension and diabetes mellitus. Moreover, in their study, a PLR of 132 predicted only severe atherosclerosis with the above mentioned sensitivity and specificity. The PLR was significantly higher in the severe atherosclerosis group (183.5 ± 61.6) vs. mild atherosclerosis group (145.2 ±96.5) vs. control group (118.4 ± 40.4). Thus PLR values are more sensitive in detecting the prevalence of IHD in COPD patients in this study; however NLR values are more specific for the same.

The cross-sectional design of this study precludes the establishment of causal relationship of COPD and IHD. Diagnosis of IHD was predominantly based on echocardiography. However, all cases should be confirmed by coronary angiography (CAG) which is considered the gold standard. PLR and NLR are new biomarkers and their normal values have not yet been standardized according to age, sex and/or ethnicity. Further studies are required to establish the normal values of the separameters. The values of NLR and PLR should be monitored for long term to establish a causal relationship and to evaluate the effect of treatment on their values.

Conclusion

Cardiovascular dysfunction has a great impact on the morbidity and mortality of COPD patients. This study is first of its kind in the state of Tripura and sheds light on the prevalence of IHD among patients of COPD. Novel biomarkers like NLR and PLR are inexpensive and easily available tools and should therefore be used in all eligible cases for the prediction of ischemic heart disease. This would be helpful in resource limited settings where coronary angiography or other sophisticated tools for evaluation of atherosclerotic cardiovascular disease are not available. It can also be useful to risk stratify the patients admitted in the hospital. Further studies are required to estimate the prevalence of other cardiovascular diseases in COPD patients so as to formulate policies to raise public awareness and implement the available resources for betterment of the patients.

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