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RESEARCH ARTICLE

INCIDENCE OF ACUTE CORONARY SYNDROME AND ITS RISK FACTORS AMONG PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) exacerbation can develop acute coronary syndrome (ACS). The cardiovascular mortality and morbidity in COPD exacerbation is often under diagnosed.

Objectives: Our study assessed the incidence of ACS in patients with COPD exacerbation, the risk factors associated with it and 28 day all-cause mortality of patients with COPD exacerbation.

Methods: A prospective observational study was conducted on consecutive patients admitted with COPD exacerbation from February 2016 to August 2017. They were monitored during the hospital stay for occurrence of ACS and followed up till 28 days.

Results: 298 patients were evaluated. Incidence of ACS was 7.71%. ACS was commoner in patients with severe COPD (65.21% Vs 34.78%), diabetes mellitus (18.98% Vs 3.6%, p= 0.001) and systemic hypertension (12.5% Vs 5.44%, p= 0.03). Patients with ACS had a higher mean age (69.65 Vs 62.98yrs, p=0.0001) and mean number of previous exacerbations (1.82 Vs 1.60, p=0.032) but lower mean forced expiratory volume in 1st second (32.3ml Vs 56.25ml, p=0.001).Hypoxic patients were at higher risk for developing ACS (14.71% Vs 5.65%, p=0.013). The 28-day all-cause mortality was 15.77% and was higher among patients with severe COPD compared with mild COPD (4.36% Vs 3.35%)and those with ACS compared with no ACS (34.78% Vs 14.18%, p= 0.02).

Conclusion: Incidence of ACS in COPD exacerbation was high. More care needs to be exercised to identify cardiac events and thus reduce the mortality and morbidity of COPD patients.

Introduction:-

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world.(1) However many people with COPD do not die from respiratory diseases and cardiovascular disease accounts for nearly 30% of all deaths.(2) There is an increased risk of coronary artery disease, myocardial infarction and angina in COPD patients.(3) The risk is further increased during periods of exacerbation.(4),(5)

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COPD patients who develop acute coronary syndrome (ACS) are more likely to present with atypical chest pain and breathlessness as compared to patients without COPD.(6),(7) COPD is also associated with a late presentation (>12hours after onset of symptoms) in ACS.(8) The overlapping spectrum of symptoms may erroneously be attributed to COPD rather than ACS. These patients also have lower diagnostic marker levels including troponin and creatinine kinase.(8), thus the cardiovascular morbidity and mortality in COPD exacerbation is often under diagnosed.

COPD patients who present with ST elevation myocardial infarction (STEMI) are more likely to have an initial incorrect diagnosis and a longer median time to reperfusion compared with patients without COPD.(9) They are also more disposed to be undertreated with drugs and reperfusion strategies.(10) Heart failure and death following myocardial infarction are more likely to occur in COPD patients versus non-COPD patients. These effects are larger and pronounced in younger patients and in those with non ST elevation myocardial infarction (NSTEMI).(11)
At present, many of the cardiac events during COPD exacerbation are unrecognized despite improved tools for diagnosis and assessment. This study is aimed at evaluating the incidence of acute coronary syndrome in COPD exacerbation, to identify the factors associated and to assess the mortality which in turn would help us to exercise more care in identifying such cardiac events and help us in decreasing the mortality and morbidity of COPD patients.

Methodology:-

Study design

We conducted a prospective study in the department of pulmonary medicine, government medical college Thrissur which is a tertiary care center in Kerala from February 2016 to august 2017.Consecutive patients diagnosed as acute exacerbation of COPD satisfying the global initiative for chronic obstructive lung disease (GOLD)2017 guideline(12) were included in the study after obtaining informed consent. Patients with a previous history of cardiovascular disease and those with a diagnosis of renal failure, sepsis, myocarditis / pericarditis, acute pulmonary embolism, cardiac infiltrative diseases, congestive cardiac failure were excluded.

Data collection

Patients included in the study were interviewed personally and were monitored. Clinical symptoms, treatment & detailed exacerbation history, smoking status and clinical signs were recorded. Smoking index was calculated by multiplying number of cigarettes smoked per day and total number of years smoked. Pulse oximetry was used to record the oxygen saturation of all patients. Investigations including complete blood count, serum creatinine, serum potassium, random blood glucose and chest X-ray were done in all patients. Previously performed pulmonary function tests (PFT) were obtained. If not available, PFT was done 6 weeks after exacerbation. Study subjects were classified into 4 groups; Group A (less symptom, low risk), Group B (more symptom, low risk),Group C (less symptom, high risk) and Group D (more symptom, high risk) as per GOLD 2017 guidelines.(12) Modified medical research council (mMRC) grade was used for symptom assessment and the number of exacerbations in the previous 1 year was used for assessment of future risk of exacerbation. A score of 0-1mMRC constituted less symptom group while score of >1 formed the more symptom group. 0 or 1exacerbation not leading to hospital admission and ≥2 exacerbation or ≥1 exacerbation leading to hospital admission accounted for the low and high risk groups respectively. Electrocardiogram (ECG) was taken for all patients at the time of admission and was repeated if needed. Troponin T was measured in patients with history of typical cardiac pain or with ECG changes suggestive of myocardial ischemia. Cardiac troponin T levels were measured qualitatively within 12 to 24 hours of onset of chest pain. If troponin was done earlier than 12 hours and came as negative it was repeated. When troponin T measurement was not available in hospital, we measured serum Creatine kinase-muscle MB fraction (CKMB). ACS included myocardial infarction (MI) -both STEMI and NSTEMI- and unstable angina (UA). MI was diagnosed when symptoms of cardiac ischemia were present with new ST-T changes, or development of pathological Q waves in the ECG; in presence of elevated cardiac troponin or CK-MB. Patients with classical cardiac pain but with normal biomarkers were diagnosed as unstable angina. All patients were followed up till 28 days either in person or by telephonic conversation to assess all- cause mortality.

Data Analysis

The data was collected, coded and entered into Microsoft excel 2007. Statistical analysis was done with the software Epi Info. The demographic variables of COPD patients were expressed in rates and percentage. Association between various factors and ACS was assessed with chi-square test. If the count of any cell was less than 5, Fischer's exact test was used. The level of significance was estimated with 95% confidence intervals with p value <0.05.

Results:-

A total of 298 patients were enrolled in the study. The demographic variables of the population are enumerated in table 1. The mean age of the study population was 63.05±8.03years. Majority of the population were males among which nearly one-third was current smokers. 38% (n=113) of the study subjects were underweight and most of them consumed alcohol on a regular basis. All study participants had a forced expiratory volume in 1st second to forced vital capacity ratio (FEV1/FVC) <0.70. The mean FVC was 72.21% of predicted. Majority of the population had a moderate airway obstruction with the mean FEV1 being 57.57% of predicted. Combined COPD assessment was used to categorize study subjects into groups A, B, C or D (Figure 1).

All study subjects (100%, n=298) were dyspneic at the time of presentation and nearly one-third were hypoxic (SPO2<90%) at the time of admission. Out of the total 298 study subjects, 7.71% (n=23) developed an acute coronary syndrome. Among the acute coronary events, unstable angina was the commonest (3.69%, n=11), followed by NSTEMI (2.68% n=8) and STEMI (1.34%, n=4). Among patients who developed an acute coronary event, 65.21% (n=15) belonged to group D COPD, followed by 26.08% (n=6) in Group C and 4.34% (n=1) each in groups A and B (table 2). Univariate analysis of the various factors that could have association with ACS was performed. COPD patients with ACS had a higher mean age and previous exacerbation rate, but lower mean FEV1 as compared to patients without ACS which was statistically significant. None of the biochemical parameters were found to be significantly associated with ACS (Table 3).

Hypoxic patients (SPO2< 90%) were twice likely to have an ACS as compared to normoxic ones (SPO2 ≥ 90%) (p=0.013, odds ratio 2.87). Diabetes mellitus and systemic hypertension had significant association with the occurrence of ACS (table 4).None of the treatment modalities for COPD were found have a statistical significance to account for ACS (table 5). Upon multivariate regression analysis, all variables which were found to be significant on univariate analysis (except the mean number of exacerbation) were found to be independently associated with ACS. The 28-day all- cause mortality was 15.77% (n=47) and was higher among patients with a higher stage of COPD, that is group D (4.36% versus 3.35%). Death was more likely in a patient who developed an ACS (p=0.02, OR 3.2) (table 5)

Table 1:-Demographic profile of the study population

Variable	Total(n=298)	Male(n=285)	Female(n=13)
Mean age(in years)	63.05	68.22	62.68
Mean BMI(kg/m^2)	21.23	19.67	22.09
Current smokers	26.85%(80)	28.07%(80)	0%(0)
Alcohol consumers	66.78%(199)	69.82%(199)	0%(0)
On treatment for Diabetes	26.59%(79)	25.96%(74)	38.46%(5)
On treatment for Hypertension	32.21%(96)	30.87%(88)	61.53%(8)
On treatment for dyslipidemia	18.45%(55)	17.89%(51)	30.76%(4)

Table 2:-Incidence of ACS amongst COPD groups

COPD Groups	A	B	C	D
ACS n (%)	1(4.34%)	1(4.34%)	6(26.08%)	15(65.21%)

Table 3:-Comparison of COPD patients with and without ACS

Variable	ACS	No ACS	P value
Mean age	69.65(SD 4.97)	62.98(SD 8.03)	0.0001
Mean BMI	18.2(SD 2.93)	16.9(SD 3.10)	0.749
Mean Smoking Index	572.30(SD 372.84)	554.49(SD 317.06)	0.784
Mean number of exacerbations in previous year	1.82(SD 0.38)	1.60(SD 0.49)	0.032
Mean FEV1	32.30(SD 8.83)	56.25(SD 17.29)	0.001
Mean Hemoglobin	14.53(SD 1.53)	14.07(SD 1.40)	0.130
Mean WBC count	13,398(SD 1783)	12,420 (SD 3001)	0.120

Mean Serum Creatinine	1.27(SD 0.56)	1.13(SD 0.52)	0.636
Mean Serum potassium	4.608(SD 0.77)	4.23(SD 0.73)	0.724
Mean RBS	115.2(SD 39.66)	139.24(SD 36.54)	0.713

Table 4:-Association between known co morbidities and ACS

Known co morbidities		Total frequency n (%)	ACS		Odds Ratio (95% CI)	χ^2 (p value)
			Yes n (%)	No n (%)		
Diabetes Mellitus	Yes	79(26.5%)	15(18.98%)	64(81.01%)	6.18 (2.50-15.24)	19.16 (0.001)
	No	219(73.49%)	8(3.6%)	211(70.80%)		
Systemic hypertension	Yes	96(32.21%)	12(12.5%)	84(87.5%)	2.48 (1.05-5.84)	4.54 (0.03)
	No	202(67.79%)	11(5.44%)	191(94.55%)		
Hyperlipidemia	Yes	56(18.79%)	3(5.35%)	53(94.64%)	0.62 (0.18-2.19)	0.53 (0.46)
	No	242(81.21%)	20(8.26%)	222(91.73%)		

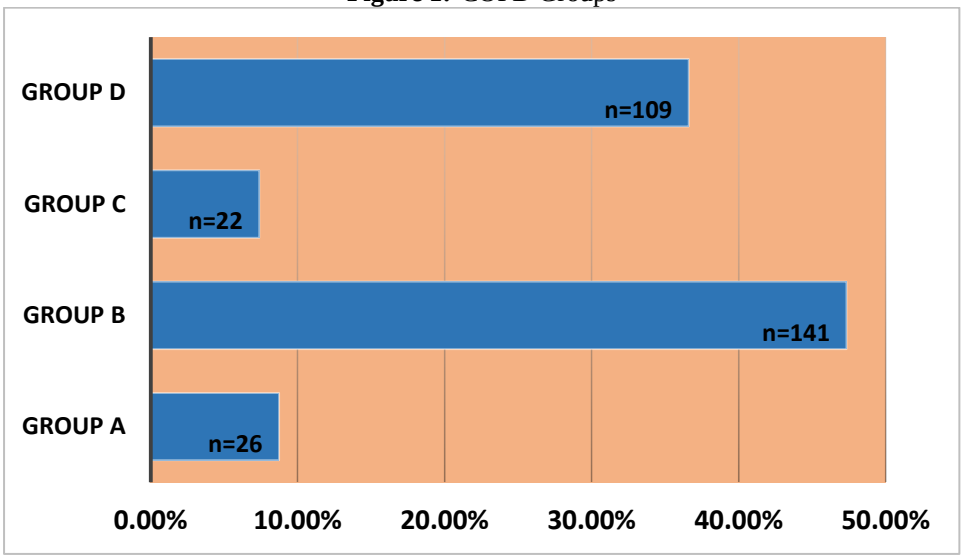
Table 5:-Association between treatments received for COPD exacerbation and ACS

Treatment Received		Total frequency n (%)	ACS		Odds Ratio (95% CI)	χ^2 (p value)
			Yes n (%)	No n (%)		
Beta Agonists	Yes	185(62.08%)	15(8.11%)	170(91.89%)	1.15 (0.47-2.82)	0.104 (0.74)
	No	113(37.92%)	8(7.08%)	105(92.92%)		
Anticholinergic	Yes	277(92.95%)	20(7.22%)	257(92.78%)	0.46 (0.12-1.72)	1.36 (0.24)
	No	21(7.05%)	3(14.29%)	18(85.71%)		
Systemic Steroids	Yes	55(18.46%)	1(1.81%)	54(98.18%)	0.186 (0.02-0.41)	2.35 (0.12)
	No	243(81.54%)	22(9.05%)	221(90.94%)		
Methyl xanthine	Yes	294(98.60%)	22(7.48%)	272(92.52%)	0.2 (0.02-2.43)	1.7 (0.17)
	No	4(1.34%)	1(25%)	3(75%)		
Non Invasive Ventilation	Yes	104(34.90%)	11(10.58%)	93(89.42%)	1.79 (0.76-4.22)	1.8 (.0.17)
	No	194(65.10%)	12(6.19%)	182(93.81%)		
Invasive ventilation	Yes	36(12.08%)	1(2.78%)	35(97.22%)	0.31 (0.04-2.38)	0.7 (0.39)
	No	262(87.92%)	22(8.40%)	240(91.60%)		

Table 6:-Association of ACS and 28-day all-cause mortality

		Deaths n (%)		Total	Odds Ratio (95% CI)	χ^2 (p value)
		Yes	no	n (%)		
ACS	Yes	8(34.78%)	15(65.22%)	23(7.71%)	3.2 (1.2-8.1)	5.31 (0.02)
	No	39(14.18%)	236(85.82%)	275(42.28%)		

Figure 1:-COPD Groups



Discussion:-

COPD is one of the leading causes of death and will become the third most common cause of death by 2020. Cardiovascular disease is a frequent co morbidity in COPD patients and accounts for 30% of all deaths in COPD. Inflammation, endothelial dysfunction, and increased arterial stiffness, in addition to shared risk factors, are all thought to contribute to cardiovascular risk in COPD.

The incidence of acute coronary syndrome in the present study was 7.71%. This was slightly lower as compared to the study conducted by McAllister et al who reported that 1 out of every 12 patients (8.33%) admitted for COPD acute exacerbation met the universal criteria for diagnosis of Myocardial infarction.(13) Previous studies have reported the prevalence of elevated troponins during COPD exacerbation.(14) McAllister and colleagues reported that most of these patients with raised troponin also had chest pain and serial ECG findings and met the universal criteria for diagnosis of MI. They concluded that a substantial proportion of these myocardial infarctions would have developed secondary to increased myocardial demand/reduced oxygen supply, that is type 2 Myocardial Infarction. We did not do troponin in all patients, but did it in patients with cardiac pain or ECG changes of ischemia.

Acute coronary syndromes, in the present study were accounted by unstable angina, Non STEMI and STEMI in the decreasing order of frequency. Bursi et al have reported that COPD patients more frequently presented with NSTEMI than STEMI and that they have smaller biomarker increase.(8)

In the present study, ACS was more frequent in patients with a severe stage of COPD namely groups C & D. Patients who developed an acute coronary event during hospital stay, had a higher mean age and mean number of COPD exacerbations but lower mean FEV1 as compared to patients without ACS. Zureik et al have earlier reported that low FEV1 is an independent risk factor for atherosclerosis and coronary artery disease(15). In the "Men Born in 1914" Study, Engstrom and colleagues compared the incidence of coronary events among those in the highest FEV1 /FVC quintile with those in the lowest FEV1/FVC quintile over a period of 13 years. Coronary events were on an average 73% higher in the latter (after adjustment for tobacco consumption, former smoking, alcohol consumption, angina pectoris, physical activities, and diabetes).(16) A population based study conducted by Ulf Nilsson and colleagues reported that the prevalence of self-reported ischemic heart disease and probable ischemic ECG changes was associated with the severity of COPD as assessed by spirometry.(17) These data indicate that reduced lung function is an independent risk factor for coronary events.

The present study could not find any significant association between treatment received for COPD exacerbation and ACS. Tachycardia has been proven to be an independent risk factor for cardiovascular mortality in general population. Therefore theoretically, the liberal use of bronchodilators could exacerbate the underlying cardiac disease in COPD. However studies identifying potential adverse effects of bronchodilator use on cardiac disease in

the COPD population are small. The evidence that short-acting bronchodilators have adverse cardiac effects is currently lacking. Another study conducted by Huiart et al have reported that use of oral corticosteroids was associated with higher risk of Myocardial infarction(4) which the present study could not find.

Our study looked at the short term incidence of ACS during hospital stay and 28 day all-cause mortality. The overall 28 day all-cause mortality was 15.77%. This is comparable with previous studies that have reported the short term mortality in COPD exacerbation to be between 1.8 to 20.4%.(18) Mortality was higher among patients with ACS. This is in accordance with the systematic review and meta-analysis conducted by Rothnie KJ et al who concluded that there was strong evidence for increased risk of death during follow up in COPD patients with acute myocardial infarction.(19)

Limitations of present study are

1. ECG changes are common in COPD both in the stable state as well as during exacerbation. Also, cardiac troponin is frequently elevated in COPD even in the absence of overt cardiovascular disease which is probably due to the right ventricular strain in COPD. Hence there is a possibility that false positives might have crept into the results.
2. MI was diagnosed when symptoms of ischemia were present along with new ST-T changes or pathological q wave in ECG and a positive troponin T card test. We did not rely on the universal definition for diagnosis of MI since we could not demonstrate a rise/fall in troponin levels; rather a single point qualitative measurement was made.
3. The present study was a single-centre study with small sample size; hence the results cannot be extrapolated to the general population.

Conclusion:-

Incidence of ACS in COPD exacerbation was 7.71%. ACS was more frequent in patients with severe stage of COPD. The risk was higher in older patients, those with hypoxia, low FEV1 and co morbidities like diabetes mellitus and systemic hypertension. The 28-day all-cause mortality was 15.77% and was significantly higher among patients with ACS (34.78%).

The results of the present study would enable pulmonologists and emergency care physicians to positively look for acute coronary events in otherwise innocuous COPD exacerbation so that more care can be exercised ,which may result in decreased mortality & morbidity. However further studies are warranted in this regard.

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