A Study on Elevation of Troponin I Levels in Acute Exacerbation of COPD and Its Correlation with Clinical Outcome

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ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, and causes significant morbidity. Cardiovascular compromise is often associated with COPD, especially in acute exacerbations. The purpose of this study is to find out the incidence of elevation of troponin I levels in acute exacerbation of COPD patients and measuring the outcome in terms of need for ventilation (both invasive and non-invasive), length of hospital stay & mortality.

METHODS

This was a prospective analytical study done on 30 patients with acute exacerbation of COPD who were admitted in Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamil Nadu from December 2015 to June 2016. Troponin I levels were estimated for all patients on admission. A cut off value of more than 34.2 pg/ml was considered as elevation. A written informed consent was obtained. Clinical outcomes were studied by doing echocardiogram to measure the pulmonary artery systolic pressures (PASP), the need for mechanical ventilation (both invasive and non-invasive), length of stay in the hospital and mortality.

RESULTS

The pulmonary artery systolic pressures were 52 mm of Hg vs 40.3 mm Hg ($P < 0.002$), length of hospital stay was 9.67 vs 6.63 days ($P < 0.027$), patients who required ventilatory support were 13 out of the 30 and the mean duration of ventilation was higher in troponin I elevated patients 5.67 vs 3.57 days ($P < 0.0015$) and mortality was higher in patients with increased troponin I levels (2 deaths) when compared to patients with normal troponin I levels (1 death)and is statistically significant ($P < 0.001$).

CONCLUSIONS

There was a significant elevation of troponin I in acute exacerbation COPD patients. Our study concluded that the presence of elevated levels of troponin I in acute exacerbation of COPD is associated with increased morbidity in terms of increased need for mechanical ventilation, intensive care unit (ICU) stay and mortality.

KEYWORDS

Cardiac Biomarker, NIV, PASP, Troponin I

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DOI: 10.18410/jebmh/2021/319

How to Cite This Article:
Devi CN, Dhivya E, Ramakrishnan C. A study on elevation of troponin I levels in acute exacerbation of COPD and its correlation with clinical outcome. J Evid Based Med Healthc 2021;8(21):1691-1695. DOI: 10.18410/jebmh/2021/319

Submission 07-10-2021,
Peer Review 17-10-2021,
Acceptance 02-04-2021,
Published 24-05-2021.

BACKGROUND

The burden of COPD is rising due to continued exposure to risk factors that trigger COPD and the increased life expectancy of the people.[1] World Health Organization (WHO) predicts that in future, COPD will become the third leading cause of mortality by 2030.[2]

According to WHO, 251 million people globally suffer from COPD out of which 65 million have moderate to severe COPD. On an average, 3.2 million deaths occur worldwide because of COPD and its complications, and more than 90 % of COPD deaths occur in low- and middle-income group from developing countries. Causes that are mostly attributed being poor socio-economic status, changing age structure, life style modifications which includes smoking, tobacco usage, physical inactivity, faulty diet patterns and exposure to environmental pollutants. Cardiovascular compromise is often associated with COPD, especially in acute exacerbations and is found to be a leading cause of mortality and morbidity.

COPD exacerbations are defined as, "An event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute on onset, and may warrant a change in regular medication in a patient with underlying COPD"[1] Sin et al. estimated the percentage of patients with COPD who die of cardiovascular disease to be in the range of 12 – 37 %.[3]

COPD is associated with a higher prevalence of a 10-year cardiovascular risk assessment > 20 % in those aged 55 – 74 than the general population.[4]

Tools for detecting changes in cardiovascular system can be met with electrocardiogram, echocardiogram, plasma biomarkers which help to assess the severity of acute exacerbation of COPD and provide prognosis. For example, elevation of troponin was associated with increased severity of the exacerbation.[5]

Baillard et al. showed that there was an elevation in troponin I in 18 % of patients studied.[6] However, mechanism of elevation of cTnI (Troponin I) in acute exacerbation of COPD is not known. Tachycardia, hypotension, septicaemia related to secondary infection in COPD, septic shock, systemic inflammatory response can be attributed to release of troponin I into the circulation from the cytosolic pool of myocytes in cardiac muscle. The increased cardiac oxygen demand and reduced diastolic filling time, decreases the coronary perfusion. There is a relative supply demand mismatch in the myocardium. These are proposed to be one of the reasons that can cause myocardial damage to some extent, thereby increasing the level of troponins. This enzyme is specific for cardiac muscle injury as a result of myocytolysis that occurs with autonomic dysfunction. The reasons for its elevation that could be proposed are increased work of breathing, worsening of pulmonary hypertension, increased left ventricle (LV) after load due to more negative intra thoracic pressure, hypoxemia, and hypercapnia.[7] The presence of pathophysiological factors that stimulate stretch-reactive integrins, viable cardiomyocytes release cardiac troponin I into circulation.

Objectives

The study was done to find out the association between troponin I in acute exacerbation COPD patients and its relation with morbidity and mortality there by finding out the need for mechanical ventilation, both invasive and non-invasive and the duration of hospital stay.

METHODS

This is a prospective analytical study conducted among 30 patients of acute exacerbation of COPD who were admitted in Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamil Nadu from December 2015 to June 2016. Sample size was estimated using the formula

$$n = N * X/\,(X + N - 1), where, X = {Z_{a/2}}^2 * p * (1-p)\,/\,\mathrm{MOE}^2, \text{and } Z_{a/2}$$

Is the critical value of the normal distribution at α/2 (e.g. for a confidence level of 95 %, α is 0.05 and the critical value is 1.96), MOE is the margin of error, p is the sample proportion, and N is the population size. Sample size was 30 patients those who presented to our hospital in emergency ward with acute exacerbation of COPD who fulfil the inclusion criteria were included in the study. Sampling was a non-probability sampling technique out of which purposive sampling was used in the study. A written informed consent was obtained after explaining the nature of the study. The study included COPD cases with acute exacerbation of both genders. For all the patients, serum sample of cardiac troponin I was done on admission. Those who had significant elevation that is more than 34.2 pg/ml were subjected to echocardiogram to estimate the pulmonary arterial systolic pressure (PASP) that would have had any impact in the due course of the disease or may accelerate its progression. Further, the need for mechanical ventilation either invasive or non-invasive was studied along with their disease progression leading onto recovery or mortality. The length of hospital stay was taken into account for all the patients.

Inclusion Criteria

1. All COPD patients with acute exacerbation admitted in medical emergency room more than 30 years of age,
2. Patients who were willing to participate in the study.

Exclusion Criteria

Patients with H/O coronary artery disease, chronic systemic illness like chronic kidney disease, decompensated chronic liver disease, those with marked hemodynamic instability, presenting with cardiac arrest on admission, with prior H/O lung surgeries, genetic disorders (cystic fibrosis, alpha 1 antitrypsin deficiency) causing lung function compromise were excluded from the study.

Ethical Committee Approval

Obtained by institutional ethical committee. With reference number bearing IEC no 4531 / ME / I / P. G / 2014

Study Protocol

A detailed history and clinical examination was performed for all the patients who were presented with acute onset of breathlessness to the medical emergency room. Patients who were diagnosed with acute exacerbation of COPD and satisfied the inclusion criteria were included in the study. A special enquiry on personal history like, smoking habits, alcoholism, and other co morbid illness like hypertension, diabetes mellitus was made. Serum troponin I level was checked at the time of admission in all the patients and they were followed up with echocardiogram to find the pulmonary arterial systolic pressure, the length of hospital stay, need for mechanical ventilation (either non-invasive ventilation or invasive ventilation) and mortality.

Statistical Analysis

Statistical analysis was performed using statistical package for social sciences (SPSS) v.21.0 software and Microsoft Excel. Numerical data were summarized by measures of central tendency: mean and standard deviation. Qualitative data was analysed with descriptive statistics and a two-way univariate analysis was used for comparing the study variables. If P – value is < 0.05 at 95 % confidence intervals, it was taken as statistical significance.

RESULTS

Mean age of the subjects in the study was 59.23 years with the youngest person being 43 years and the oldest being 74 years. Males were predominant constituting 73.33 % (22 males and 8 females) in the study. In the study population, there were 16 smokers (53.33 %). Hypertension was present in 18 patients (60 %), diabetes was present in 20 patients (66 %). Troponin I was elevated in 6 out of 30 patients (20 %) (Table:1). The pulmonary arterial pressure was measured in all the patients with a two-dimensional echocardiogram. Pulmonary hypertension was present in 80 % of patients with a mean pressure of 52 mm of Hg in patients with elevated troponin levels vs a mean pressure of 40.3 mm Hg in patients with normal troponin levels with statistical significance measured by a P value of < 0.002 (Table:2). The mean duration of hospital stay was significantly higher (9.7 days) in patients with elevated troponin I levels vs 6.6 days in others with a P value of < 0.027 (Table:2). Patients who required ventilatory support were 13 out of the 30 (43.33 %) and the mean duration of ventilation was higher in troponin I elevated patients 5.7 days vs 3.6 days in others with a P value of < 0.0015 (Table:2) and three deaths were reported. Mortality was higher in patients with increased troponin I levels (2 deaths) when compared to patients with normal troponin I levels (1 death) and is statistically significant (P < 0.001).

Group	TROP -I				Total
	Normal		Elevated		
	N	%	N	%	
Acute exacerbation	24	80	6	20	30

Table 1. Troponin I Levels in Acute Exacerbation of COPD

Variables	Troponin I		t-Value [95 % CI]	P - Value
	Normal (n = 24)	Elevated (n = 6)		
PASP (Mean ± SD)	**40.3 ± 8.2**	**52 ± 9.2**	**3.27**	**0.002***
Duration of hospital stay	6.6 ± 2.8	9.7 ± 2.8	2.34	0.027*
Days on ventilation	3.6 ± 0.9[$]	5.7 ± 1.6	2.86	0.015*

Table 2. Comparison of PASP, Duration of Hospital Stay, and Number of Days on Ventilation

**indicates statistically significant difference at P < 0.05,* [$]n = 7

TROP -I	Outcome		Chi Square Value	P Value
	Death n (%)	Discharged n (%)		
Normal	01 (4.17)	24 (95.8)	14.73	0.001**
Elevated	02 (33.3)	06 (66.7)		

Table 3. Troponin I Elevation and Its Association with the Outcome of the Patient

*indicates statistically significant difference at P < 0.05

DISCUSSION

During acute exacerbations of COPD, bronchoconstriction, increased mucus production and alveolar hypoxia results in elevation of pulmonary vascular resistance which leads to hypoxaemia and increased cardiac stress. Therefore, exacerbations represent an increased workload to the myocardium, and myocardial injury with release of cardiac-specific troponin I can occur. To the best of the various authors' knowledge obtained from different studies the association between troponin elevation and mortality in patients with acute exacerbations of COPD is a unique and novel finding. Moreover, it may be important for risk stratification and treatment of patients hospitalised for COPD exacerbation.

The patients selected were in the age ranging from 40 to 74 years, with a mean age of 59.23 years. Smoking and tobacco usage as risk factors were significantly associated. It is estimated that 25 % of patients with moderate to severe COPD develop pulmonary hypertension within 6 years, if they have normal PASP.[8] COPD and cardiovascular disease share common paths in terms of risk factors like ageing, smoking duration and pathophysiology. Severity and frequency of acute exacerbations of COPD can influence the occurrence of major adverse cardiovascular events. Good compliance of patients in preventing frequent exacerbations can lead to preservation of cardiac function, improvement in pulmonary vasoconstriction and stiffness of arterial walls. The presence of cor pulmonale is an ominous sign in COPD and is a major cause of mortality.[9,10] Chamber dilatations especially the right ventricle, tricuspid regurgitation and LV dysfunction as measured by poor left ventricular ejection fraction and ECG abnormalities like right bundle branch block, multifocal atrial tachycardia, right ventricular hypertrophy were present in few patients and that explains the morbidity thereby contributing to increased days of hospital stay, duration of oxygen dependence, major adverse cardiovascular events and death. The presence of emphysema causes impaired left ventricle filling.[11] An

increase in intrathoracic pressure and hyperinflation due to emphysema jeopardizes cardiac function as it decreases the biventricular preload and increases the left ventricular afterload.[12] Myocardial relaxation is also affected by chronic hypoxemia.[13] The alterations in inflammation, endothelial function and platelet reactivity associated with acute exacerbation of COPD may contribute to destabilization of underlying coronary artery disease. Troponin elevation during exacerbations could be a marker of this disease activation. This is indirectly confirmed by the higher incidence of cardiac adverse events MACCE in the first months after acute exacerbation of COPD. Hypoxia causes systemic arteriolar vasodilatation and vasoconstriction in pulmonary vessels. The haemodynamic responses of the pulmonary parenchyma to hypoxia are variable. Chronic hypoxia affects the pulmonary vasculature via both tonic vasoconstriction and vascular remodeling with myointimal hyperplasia of the pulmonary vascular bed.

Thus, in the setting of cardiovascular disease, varying degrees of hypoxia, hyperinflation of the lung, secondary erythrocytosis in view of chronic hypoxemia, increased platelet activity, loss of pulmonary vascular surface area, loss of functionally active pulmonary parenchyma are the underlying pathophysiologic factors that lead to the inexorable association of cardiovascular compromise with pulmonary hypertension. Pulmonary hypertension, elevated right ventricular filling pressure, and increased intrathoracic pressure are responsible for the dysrhythmias. There is a reported higher incidence of atrial arrhythmias in COPD patients with acute exacerbations, that can be explained by both raised right ventricular pressure and an imbalance in pro inflammatory and anti-inflammatory mediators in COPD patients.[14]

To conclude, the influence of chronic right ventricular pressure overload on the interventricular septum may also affect left ventricular filling as a result of abnormal left ventricle torsion and impaired longitudinal and circumferential strain.

In severe cases of acute exacerbation, muscle overload may occur, and hypercapnic respiratory failure may develop insidiously. After the respiratory failure sets in, the life expectancy of the patient gets compromised in addition to the induced cardiovascular homeostasis dysregulation. Prevention of frequent exacerbations not only leads to slowing down of the disease progression but also avoids cardiovascular morbidity as well as mortality.

Main aim of the study was to find out any significant association between elevation of troponin I levels in acute exacerbation of COPD and unfavourable clinical outcomes. 6 cases out of 30 had a higher troponin I levels (> 34.2 pg/ml) which had significant risk in the outcome as evidenced by increased need for oxygen both on a quantitative and qualitative basis, increased need for mechanical ventilation i.e. more patients went through NIV rather than invasive ventilation with an endotracheal intubation, more hospitalised days. A significant association based on statistical analysis with a P value < 0.005 was found. A survey found that the mortality rate in hospital was 11 % and the 1-year mortality rate was 43 % in COPD patients with acute exacerbations.[15] Mortality is substantially increased in COPD patients who require mechanical ventilation. Thus, the aim and the objectives of the study was met. Thus, cardiac troponin I was positive in 23.33 % which is having statistical significance in predicting morbidity and mortality, and it was comparable with other studies done in other parts of the world like Baillard et al. Martin et al. Chang et al. which has comparable evidence consistent with our study.

CONCLUSIONS

There is a significant elevation of troponin I in acute exacerbation COPD patients**.** Troponin I elevation is thus a prognostic indicator for predicting morbidity by means of increased need for ICU stay, mechanical ventilation necessity, hospitalization and mortality in acute exacerbation of COPD patients with a proof of statistical significance. Prognosis is poorer in troponin elevated acute exacerbation COPD patients when compared with acute exacerbation COPD with normal trop I levels. In other words, COPD patients with concomitant cardiovascular disease have increased morbidity as well as mortality of all causes. However, it is difficult to find out a risk ratio or weigh the risk benefits for a group of acute exacerbation patients. The reason being the heterogenic etiology and pathophysiologic interaction between both diseases.

Limitations of the Study

The patients were not followed up for prolonged periods in terms of further cardiovascular compromises if they had any. Subjects with varied stages of severity of COPD were included. Severity of COPD was not classified. Furthermore, the aetiology of COPD is multifactorial and heterogeneous in nature, cardiovascular derangement mainly depends on occurrence of exacerbation triggers. Long term follow-up can be more beneficial.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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