ASSOCIATION OF ELEVATED CARDIAC BIOMARKERS WITH MORTALITY AFTER ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

BACKGROUND

Cardiovascular disease is commonly seen in patients with Chronic Obstructive Pulmonary Disease (COPD). Brain Natriuretic Peptide (BNP) is a marker of ventricular dysfunction and troponin T of myocardial necrosis. Elevations of these markers have been found in many disorders, COPD being one of them.

The aim of the study is to assess the association of elevated cardiac biomarkers with the 6-month mortality in patients with Acute Exacerbation of COPD (AECOPD).

MATERIALS AND METHODS

86 patients admitted with acute exacerbation of COPD were included in this prospective study.
Cardiac Biomarkers- BNP and troponin-T were measured on admission. Patients were followed up for the next 6 months and mortality over this duration was recorded and analysed.
Statistical Analysis- Pearson X^2 testing was used.
Setting and Design- The study was conducted in the Department of Medicine, Silchar Medical College and Hospital, Silchar, Assam. It was a prospective hospital-based observational study.

RESULTS

Four groups based on the cardiac biomarker elevation pattern were seen- (1) With no elevation of cardiac biomarkers - 62.8% (54/86); (2) With elevation of troponin alone- 17.4% (15/86); (3) With elevation of BNP alone- 7% (6/86); and (4) With elevation of both BNP and troponin T- 12.8% (11/86). Over 6 months, a total of 16.27% (14/86) died. (1) In the group with no elevation- 3.7% (3/54) deaths occurred. (2) In the group with only troponin elevation- 33.3% (5/15) deaths occurred showing a statistical significance (p=0.004; RR=9.0). (3) In the group with only BNP elevation- 16.7% (1/6) deaths occurred, but were statistically insignificant (p=0.275). (4) The group with elevation of both BNP and troponin-T had- 45.5% (5/11) deaths achieving the highest statistical significance (p=0.000; RR=12.3).

CONCLUSION

In COPD patients presenting with acute exacerbation, an isolated elevation of troponin level or a combined elevation of BNP and troponin-T levels are strong predictors of mortality (9 fold and 12 fold increase respectively). However, elevated BNP in isolation is not associated with increased mortality.

KEYWORDS

Pulmonary Disease, Chronic Obstructive, Mortality, Natriuretic Peptide, Brain, Troponin.

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BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is a commonly encountered noncommunicable disease. It constitutes about 30% of all the cases seen in chest clinics and accounts for 1-2.5% of all hospital admissions in India.[1] COPD is also a major cause of morbidity and mortality throughout the world. As per W.H.O, it is the third leading cause of death worldwide behind ischaemic heart disease and stroke.[2] India contributes a significant percentage of COPD mortality, which is estimated to be amongst India contributes a significant percentage of COPD mortality, which is estimated to be amongst the highest in the world with about 5,56,000 (>20%) out of a world total of 2,748,000 annually.[3]

Developing countries like India are changing fast. Socioeconomic development, industrialisation, urbanisation,

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changing age structure and changing lifestyles have the countries at a position where they are facing an ever increasing burden of noncommunicable diseases such as COPD.[4]

COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as 'a common preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases with exacerbations and comorbidities contributing to the overall severity in individual patients.'[5]

Established risk factors for development of COPD include tobacco smoking, environmental tobacco smoke, hyperresponsiveness to various exogenous stimuli, occupational coal dust exposure, prolonged exposure to smoke produced by biomass combustion and alpha-1-antitrypsin deficiency.[6]

Acute Exacerbations of COPD (AECOPD) are a prominent feature of the natural history of COPD. Exacerbations are defined as-"an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication."[5]

The clinical severity of an AECOPD varies widely. It may be managed in the outpatient setting or maybe severe enough to require hospitalisation. If complicated by respiratory failure, intensive care including noninvasive or invasive ventilator support maybe required.[7]

Ball et al reported that AECOPD contributes considerably to the morbidity and the diminished quality of life of people afflicted with COPD. Patients who suffer the most exacerbations have significantly lower health status.[8] Kanner et al showed that exacerbation frequency predicts an accelerated decline in lung function.[9] Episodes of AECOPD have been associated with diminished physical activity and increase in cardiovascular risk, osteoporosis and neuropsychiatric complications.[7] Exacerbations of COPD have considerable impact on healthcare system at both primary and tertiary care levels as they are the major reason for antibiotic use and admissions. Additionally, such episodes lead to indirect costs because of days lost from work.[10] Most importantly, an increase in in-hospital and future mortality is seen in frequent exacerbators of COPD.[11]

A variety of stimuli may result in the final common pathway of airway inflammation and increased symptoms that are characteristic of COPD exacerbations. Factors that precipitate exacerbations of COPD are respiratory tract infection- bacterial or viral, air pollutants, interruption of maintenance therapy or resumption of smoking, pulmonary embolism, congestive cardiac failure, pneumothorax, cardiac arrhythmia, pleural effusion, lower temperature and humidity and higher barometric pressure. In 20-35% cases, no specific precipitant can be identified.[7,12,13]

Brain Natriuretic Peptide (BNP) is an established marker of left ventricular dysfunction.[14,15] It is associated with increased mortality in acute and stable heart disease. It is also increased in right ventricular overload and predicts a poor outcome in pulmonary arterial hypertension.[16,17,18]

Cardiac troponins are specific markers of myocardial necrosis.[19] Elevated troponin levels may also occur in pulmonary thromboembolism, congestive heart failure, tachyarrhythmias, myocarditis, pericarditis, sepsis and stroke.[20] Troponin elevations in these conditions reflect general myocardial injury rather than coronary arterial occlusion. Retrospective observations of troponin elevations in acute exacerbations of COPD have been made and are associated with the severity of excaerbation.[21]

Silchar Medical College and Hospital is the only referral hospital in the southern part of Assam and serves neighbouring states including Mizoram, North Tripura, West Manipur and South Meghalaya. A study on this particular subject has not been conducted in these parts before. The results of the study will help in providing prognostic information about patients admitted with COPD exacerbations. The study would lay the groundwork for further interventional studies on this subject.

Aims and Objectives

To assess the association of elevated cardiac biomarkers with the 6-month mortality in patients with Acute Exacerbation of COPD (AECOPD).

MATERIALS AND METHODS

Study Setting- The present study was conducted in the Department of Medicine, Silchar Medical College and Hospital, Silchar, Assam. It is a tertiary referral centre for patients of the different districts of the Barak Valley of Assam and nearby other North Eastern states like Tripura, Mizoram, Manipur, Meghalaya and Nagaland.

Period of Study- The present study was conducted from 1st June 2015 to 1st June 2016.

Sample Size- A total of 86 patients admitted in the Medicine Ward at SMCH were included in the study after fulfilment of the inclusion and exclusion criteria.

Study Design- The study was a hospital-based prospective observational study.

Methodology- All the patients with clinical features suggestive of Chronic Obstructive Pulmonary Disease (COPD) such as progressive dyspnoea, chronic cough, chronic sputum production with history of exposure to risk factors or a family history of COPD were assessed. Out of these, the patients fulfilling the criteria for Acute Exacerbation of COPD (AECOPD) were enrolled. AECOPD was diagnosed as per the criteria put forth by Anthonisen et al.

Presence of any two of the following symptoms-

- Increased cough,
- Increased purulence and/or volume of expectorations, and
- Increased severity of dyspnoea.

These patients were immediately treated and stabilised. Informed and written consent was obtained from the patients.

A detailed clinical history was taken and complete physical examination was done in all cases. A spirometry was performed on all patients along with bronchodilator reversibility testing. A post-bronchodilator FEV_1/FVC of <0.7 confirmed the diagnosis of COPD as per the GOLD 2015 guidelines. Severity of COPD was assessed using FEV_1% predicted values. Complete blood count, renal and liver function tests, cardiac biomarkers (BNP and troponin I and T), chest radiograph, ECG and 2D-echocardiography were done in all the patients.

Patients were followed up over the next 6 months and mortality over this duration was recorded.

Inclusion Criteria

All patients above 18 years of age diagnosed with COPD as per GOLD criteria presenting with acute exacerbation were included in the study.

Exclusion Criteria

1. Known cases of malignancy or immunosuppression.
2. Tuberculosis.
3. Known cases of heart failure.
4. Pneumonia.
5. Asthma.
6. Unwilling patients.

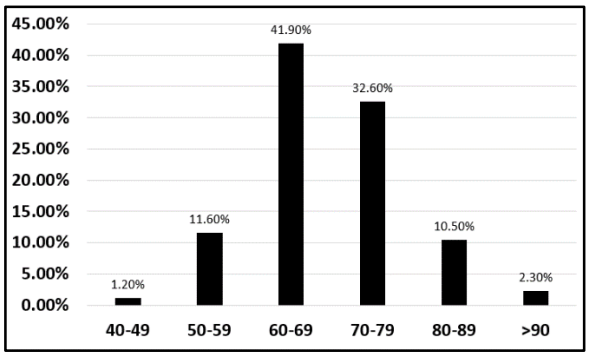
Ethical Clearance- Ethical clearance for the study was taken from the Ethical Committee of Silchar Medical College and Hospital, Silchar, Assam.

The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Revised Helsinki Declaration of 2000.

Statistical Analysis- The data collected were compiled, tabulated and analysed in terms of descriptive statistics using SPSS version 17.0 software. Continuous variables were presented as mean ± SD and categorical variables were expressed as frequencies and percentages. Categorical data between the groups were compared using Chi-square test. A p value <0.05 was considered as statistically significant.

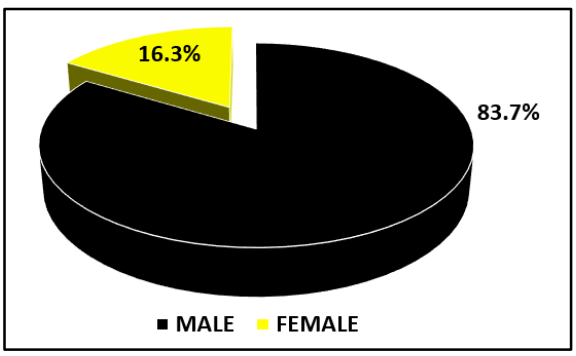
RESULTS AND OBSERVATIONS

Out of a total of 86 patients, majority of the cases were in the age group 60 to 69 (41.9%).



Graph 1. Bar Graph Showing Age Distribution of Patients

Out of all the patients, majority were males (83.7%), whereas 16.3% were females.



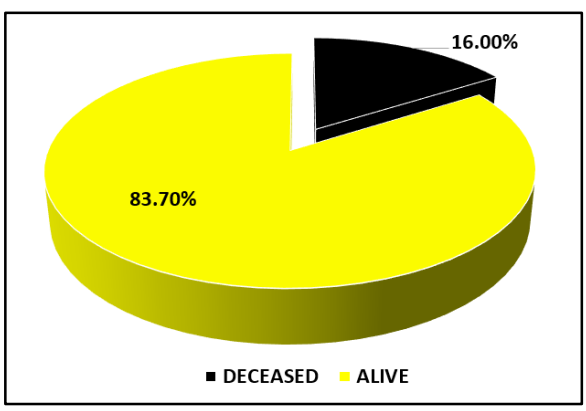
Graph 2. Pie Diagram Showing Sex Distribution of COPD Cases

Out of all the patients, majority showed no elevation of biomarkers (62.8%). Only troponin I was seen elevated in 17.4% cases, whereas only BNP elevation was present in 7% cases. 12.8% of the cases showed elevation of both BNP and troponin I.

Biomarker	Number	Percentage
BNP and troponin elevated	11	12.8%
Only troponin elevated	15	17.4%
Only BNP elevated	6	7%
No elevation	54	62.8%
Total	**86**	**100%**

Table 1. Pattern of Elevation of Biomarkers

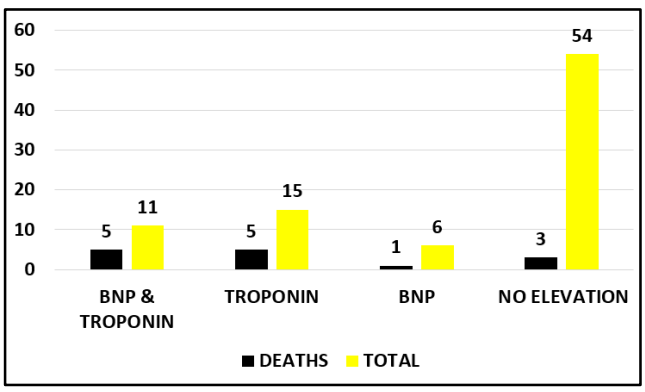
Out of all the patients, 14 patients (16.3%) expired within the next 6 months.



Graph 3. Pie Diagram of the Mortality in the COPD

Biomarker	Total Cases	Deaths (Number)	Deaths (%)	P value
BNP and troponin elevated	11	5	45.5%	<0.05
Only troponin elevated	15	5	33.3%	0.004
Only BNP elevated	6	1	16.7%	0.275
No elevation	54	3	3.7%	
Total	**86**	**14**	**100%**	

Table 2. Distribution of Deaths as per the Biomarker Elevation Pattern



Graph 4. Bar Graph Showing Distribution of Deaths as per the Biomarker Elevation Pattern

DISCUSSION

Isolated Elevation of Troponin T

In the present study, elevated levels of troponin T were significantly associated with an elevated mortality by the end of six months (p=0.004; RR=9.0).

In the study conducted by Chang et al, data on 244 subjects was collected over a period of one year.[22] 30-day mortality was calculated in these patients. Elevated troponin levels were significantly associated with increased mortality.

In the study conducted by Baillard et al, a significant association was noted between an elevated cardiac troponin T level on admission and the in-hospital mortality in AECOPD cases.[23]

Brekke et al conducted a study on this subject for a median period of about 1.9 years. Troponin T levels measured on admission were found to be strong independent predictors of mortality in their subjects.[24]

These findings are in agreement with the findings of the present study.

However, in the study conducted by Noorain et al, elevated troponin T levels were not found to predict in-hospital mortality. They were associated with the need for ICU admission and ventilator support.[25]

This difference between the present study and the study by Noorain et al maybe because of the fact that the present study included both deaths that occurred after discharge as well as those that occurred in-hospital.

Isolated Elevation of BNP

In the present study, isolated elevation of BNP level was not found to predict mortality by six months (p=0.275).

In the study by Stolz et al, they found elevated BNP levels to indicate the need for ICU admission, but no significant association was found with early or late mortality.[26]

This is in accordance with present study.

However, the study by Chang et al showed a significant association between elevated BNP and mortality.[22]

Combined Elevation of Troponin T and BNP

In the present study, combined elevation of Troponin T and BNP were significantly associated with increased mortality by the end of six months (p<0.05; RR=12.3).

This finding is in tally with the study conducted by Chang et al.[22]

The presence of elevated biomarkers in patients of AECOPD are strong predictors of mortality in patients. All such patients should be advised regular follow up after discharge. They should be counselled regarding the elevated risk of mortality. Advice regarding smoking cessation, inhalational steroid use and domiciliary oxygen use should be offered. In case additional indications are present, surgical interventional measures such as lung volume reduction surgery should be offered.

CONCLUSION

In COPD patients presenting with acute exacerbation, an isolated elevation of troponin T level or a combined elevation of BNP and troponin T levels are strong predictors of mortality (9-fold and 12 fold increase, respectively). However, elevated BNP levels in isolation are not associated with increased mortality.

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