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Original Research Article

Cardiac troponin I as mortality predictor in acute exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

Background: Comorbidities are important determinants of outcome and quality of life of patients with chronic obstructive pulmonary disease (COPD). The risk of cardiovascular events in COPD patients is three to five-fold high. COPD is often associated with right ventricular hypertrophy and pulmonary hypertension. Various studies have associated levels of cardiac troponin I (cTnI) with severity and duration of acute exacerbation of COPD (AECOPD). The objective of the present study was to assess the usefulness of serum cTnI as mortality predictor in AECOPD patients.

Methods: An observational, prospective and non interventional study was conducted in 50 patients with AECOPD admitted in the pulmonary medicine emergency or ward of a tertiary care hospital of Northern India. AECOPD was diagnosed according to Global Initiative for chronic obstructive lung disease guidelines. cTnI levels were estimated within 24 hours of admission by method based on chemiluminiscence along with routine investigations. Levels ≥ 0.01ng/ml were taken as positive. The patients were followed up for 30days for outcome in terms of mortality and morbidity. Data was entered and analyzed by SPSS package and two sided p values<0.05 were considered statistically significant.

Results: The serum cTnI was found to be positive in 34% of patients with AECOPD. The in- hospital mortality was significantly low in patients having cTnI <0.01ng/ml as compared to patients with cTnI ≥0.01ng/ml. The patients with cTnI levels ≥0.01ng/ml had significantly higher mean PaCO2 levels and higher requirement for invasive or noninvasive ventilation during hospital stay as compared to patients having cTnI <0.01ng/ml (p=0.04 and 0.016 respectively).

Conclusions: Levels of cTnI≥0.01ng/ml may be considered as a biomarker to predict mortality in AECOPD patients.

Keywords: AECOPD, cTnI, Mortality, Outcome

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. The World Health Organization has predicted that by 2020, COPD will become the third leading cause of death and fifth leading cause of disability worldwide.[1] It has considerable impact on health care system at both primary and tertiary care levels and is an important public health challenge that is both preventable and treatable. COPD is nowadays considered as a chronic inflammatory disease with extra pulmonary manifestations. Cardiovascular diseases, osteoporosis, lung cancer, diabetes, metabolic syndrome and depression are amongst a few of them.[2] Cardiovascular disease is a major morbidity in patients with COPD and is associated

with poorer outcomes in COPD exacerbations.3 The Lung Health Study conducted on 6000 AECOPD patients predicted that cardiovascular diseases were the leading cause of hospitalization and second leading cause of mortality in these patients.[3]

Cardiac biomarkers, such as cardiac troponins were initially used for evaluation of patients with cardiac ischemia and congestive heart failure and elevated levels formed a major criterion for diagnosis of myocardial infarction. In right ventricular failure, cardiac troponins are suspected to be elevated secondary to right ventricular ischemia or microinfarction resulting from increased wall tension, metabolic demand and reduced coronary perfusion with or without atherosclerosis.[4] Various studies have reported increase of cardiac troponins in conditions like left ventricular hypertrophy, myocarditis , pericarditis, pulmonary thromboembolism etc.[5] cTnI, which is a component of contractile proteins, is cardio specific and highly sensitive marker for cardiac injury. Its levels do not increase in myopathic states, after acute skeletal muscle injury and remain normal in the absence of cardiac injury.[6]

In AECOPD, there is increased cardiac burden even in the absence of cor pulmonale. Prompt diagnosis of compromised cardiac function in these patients remains difficult because of nonspecific signs and symptoms and echocardiography may not always be feasible. Therefore, there is a need for biomarkers, not only to confirm cardiac involvement but also to predict the severity and outcome. In developing countries like India, outcome estimation is particularly important because of high costs of treatment and resource paucity. The most critical decisions are taken in the very first hours after admission. Finding a simpler and more readily available indicator of severity to assist in decision making would be of paramount importance.

cTnI has been recognized as a predictor of outcome in various critically ill patients but very little data is available addressing the association between cTnI and outcome in patients hospitalized for AECOPD.[7]

The present study was planned to prospectively analyze the relationship between cTnI and mortality in study group comprising of AECOPD patients.

METHODS

The study design was **o**bservational, prospective and non interventional. 50 patients of AECOPD who were admitted in pulmonary medicine emergency or ward formed the subjects of the study (calculated with 4.1% COPD prevalence and 90% confidence interval). AECOPD was diagnosed according to Global Initiative for chronic obstructive lung disease guidelines.[8] The patients with any severe systemic disease like hepatic, renal disorders etc. were excluded from the study. The informed written consent was obtained from all the patients. The study was approved by the Institutional Research and Ethics Committee.

Detailed medical history was taken and general physical examination was done for every patient at the time of admission. Blood samples were taken within 24 h of admission to analyse serum cTnI levels along with routine investigations. Cardiac troponin I levels were estimated by chemiluminiscence method on Advia Centaur-XP. The analytical and functional sensitivities of cTnI- ultra assay were 0.006ng/ml and 0.01ng/ml respectively. The serum concentration of cTnI≥0.01ng/ml was considered to be positive.[9]

Patients were followed up for 30 days for mortality and morbidity in terms of length of hospital stay. Data was entered and analyzed by SPSS package and two sided p-values<0.05 were considered statistically significant. Results on continuous measurements are presented as mean±standard deviation and results on categorical measurements are presented in numbers (%). Student's t test has been used to find the significance of study parameters on continuous scale and chi square test has been used to find the significance on categorical scale between two or more groups. Normality of the data was tested with a one-sample Kolmogorov-Smirnov test to indicate the appropriateness of parametric testing. Survival curve was constructed using the Kaplan-Meier method and compared with the log-rank test.

RESULTS

Demographic data of the study population is shown in Table 1.

Table 1: Demographic profile of the study group (n=50).

Demographic profile	
Sex, n (%)	
Male	39 (78%)
Female	11 (22%)
Age (years, mean±SD)	58.44±16.24
Smoking status, n (%)	
Current smokers	15 (30%)
Exsmokers	21 (42%)
History of chullah exposure	4 (8%)
Nonsmokers	10 (20%)
Comorbidities, n (%)	44 (88%)
On examination, n (%)	
Wheeze	33 (66%)
Crepitations	20 (40%)
mMRC scale of breathlessness	0-II 35 (70%), III-IV 15(30%)
Treatment, n(%)	
Invasive/noninvasive ventilation	18 (36%)
Long term oxygen therapy	5 (10%)

cTnI levels were found to be positive in 17 patients and <0.01ng/ml in 33 patients of AECOPD. The in- hospital mortality was significantly low (p=0.008) in patients having cTnI<0.01ng/ml as compared to patients with cTnI≥0.01ng/ml (Table 2).

Table 2: Crosstabulation showing relationship of cTnI with outcome.

			Outcome		Total	Chi square
			Death	Survived		
cTnI	<0.01	Count	2	31	33	p=0.008
		% within cTnI	6.1%	93.9%	100.0%	
		% within Outcome	25.0%	73.8%	66.0%	
	≥0.01	Count	6	11	17	
		% within cTnI	35.3%	64.7%	100.0%	
		% within Outcome	75.0%	26.2%	34.0%	
Total		Count	8	42	50	
		% within cTnI	16.0%	84.0%	100.0%	
		% within Outcome	100.0%	100.0%	100.0%	

The distribution of cTnI levels in patients of study group categorized according to survival and death within 30 days of hospitalization is shown in Figure 1. Baseline characteristics and laboratory investigations of patients in both the groups are compared and shown in Table 3. The mean PaCO2 levels in patients with cTnI<0.01ng/ml were low as compared to levels in patients with cTnI≥0.01ng/ml and the difference was found to be statistically significant (p=0.04). The requirement for invasive or noninvasive ventilation during hospital stay was significantly higher in patients having cTnI ≥0.01ng/ml as compared to requirement in patients having cTnI< 0.01ng/ml (p=0.016).

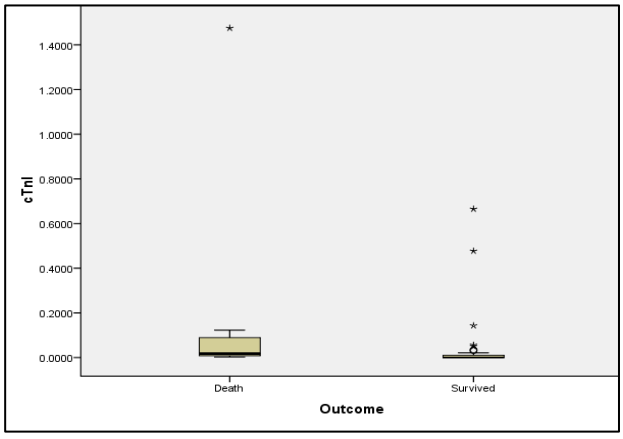

Figure 1: Boxplot showing distribution of cTnI [ng/ml] in the study group.

No statistically significant difference was observed between cTnI levels with regard to age, sex, smoking, alcohol intake, severity of exacerbation, length of hospital stay, tachycardia and presence of comorbidities (p>0.05). Kaplan Meier survival curve was plotted according to cTnI status in the study group (Figure 2) and log rank test was found to be highly significant (p=0.004).

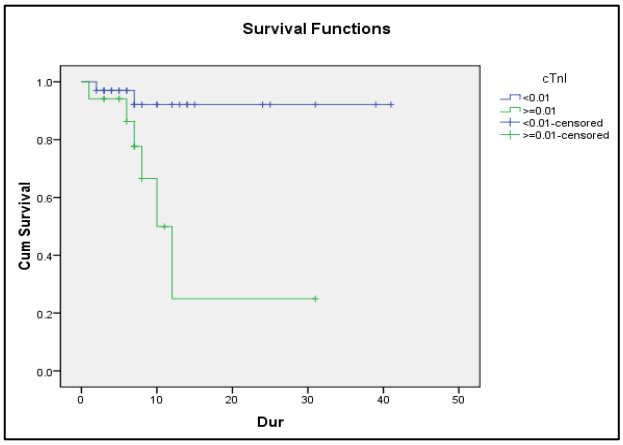

Figure 2: Kaplan Meier survival curve for patients with acute exacerbation of chronic obstructive pulmonary disease stratified according to cTnI status [Log Rank (Mantel-Cox) chi square=8.256, p=0.004].

DISCUSSION

COPD involves a chronic inflammation that leads to narrowing of small airways and alveolar wall destruction. This is carried out by inflammatory mediators like serine proteases, metalloproteinases etc.[10] Amongst various complications of COPD, cardiovascular disease is being increasingly recognized as an important cause of morbidity and a predictor of in-hospital mortality in these patients as acute respiratory failure in patients may lead to right or left ventricular failure. It was found in one of the studies that 12-37% of patients of COPD died of cardiovascular diseases.[11] cTnI is a highly cardio specific protein which increases in myocardial infarction. However, many studies have shown its increase in certain

other critical illnesses like sepsis, renal failure, trauma, stroke etc.[5] It is not clear that how diverse group of diseases can lead to troponin release but recently proposed hypothesis include paracrine mediated increase in cell membrane permeability and catecholamine induced cellular injury.[12] The present study was planned to prospectively analyse whether cTnI could predict mortality in patients with AECOPD.

Table 3: Difference in baseline characteristics and laboratory data between patients having cTnI<0.01ng/ml and cTnI≥0.01ng/ml.

	cTnI <0.01ng/ml; n=33	cTnI≥ 0.01ng/ml; n=17	P value
Age (years,mean±SD)	59.15±16.6	57.06± 15.92	0.671
Sex (M/F)	27/6	12/5	0.475
Presence of comorbidity no. (%)	28 (84.8%)	16 (94.1%)	0.339
Length of hospital stay (days)	12.14±10.50	9.46±8.41	0.425
Invasive or noninvasive ventilation no. (%)	8 (24.2%)	10 (58.8%)	0.016*
PaO2 (mmHg)	82.75±37.68	70.27±23.10	0.218
PaCO2 (mmHg)	41.43±10.42	49.40±16.92	0.04*

In the present study, no significant difference was found between mean age of patients with positive cTnI and patients with cTnI levels <0.01ng/ml (p=0.671). This finding is in agreement to results put forward by other authors who could not find any significant difference between positive and negative cTnI levels as regards to age.[4,13] However, Harvey and Hancox reported a significant difference (p=0.001) in the mean age of cTnI positive as compared to cTnI negative patients.[14] No association was found between cTnI levels with sex (p=0.364) and smoking (p= 0.082) in the present study. Similar findings have also been reported in some other studies.[9,15]

Amongst 50 patients included in the study, cTnI was found to be positive in 34% of the patients. There is another study which reported positive cTnI in 32% of patients of AECOPD. This suggests that cardiac injury exists in patients with AECOPD.[15] It has been hypothesized that in severe COPD, hypoxia can cause pulmonary hypertension by mediating contraction of small pulmonary arteries. Tachycardia and ventilation perfusion mismatch also lead to cardiac stress.[16] The results of the present study reinforced this fact as the mean PaO_2 levels in patients with positive cTnI levels were found to be less as compared to patients with cTnI<0.01ng/ml. However, this association was not found to be statistically significant (p=0.218).

cTnI is a specific protein for cardiac muscle injury. Potential mechanisms for cardiac injury may include acute elevation of pulmonary arterial pressure secondary to hypoxemic vasoconstriction with subsequent right ventricular distension, tachyarrhythmia such as atrial fibrillation and cardiac damage mediated by sepsis or metabolic stress due to hypoxia and acidosis.[14] However, cTnI increase has been attributed to increased work of breathing, increased left ventricular afterload due to more negative intrathoracic pressure, worsening of pulmonary hypertension, hypoxemia and hypercapnoea.[13] In the present study, a significant increase in $PaCO_2$ levels was found when patients having cTnI≥0.01ng/ml were compared to patients having cTnI<0.01ng/ml. Another study also reported association of elevated troponin with lower pulse oximetry and hypercapnoea.[9]

In the present study, need for invasive or noninvasive ventilation was found to be significantly high (p=0.016) in patients with positive cTnI as compared to patients having levels of cTnI<0.01ng/ml. This finding is in agreement with results put forward in other studies where the authors have reported a statistically significant difference in cTnI positivity between patients who needed ventilation and those who did not.[4,17]

The results of the present study support the fact that positive cTnI levels are associated with increased mortality in patients with AECOPD. Among 33 patients who were having cTnI<0.01 ng/ml, 31 (93.9%) survived whereas out of 17 patients who had cTnI≥0.01ng/ml, 11 survived (64.7%). In another prospective study ,the authors have reported that to predict death, cTnI higher than 0.5ng/ml has positive predictive value of 62% and negative predictive value of 83%.[13] It has been observed that with a cut off value of ≤0.055ng/ml, cTnI has sensitivity and specificity of 75% and 68% respectively as regards survival with a negative predictive value of 91.7%.[9] Martin et al have also found that elevated cTnI levels were predictors of 18 month overall survival in patients hospitalized for AECOPD.[18]

CONCLUSION

In conclusion, cTnI≥0.01ng/ml in AECOPD patients may predict mortality and indicate cardiac dysfunction in these patients. Thus, assessment of cTnI levels at the time of admission, may be done to identify the patients at increased cardiac risk. Early diagnosis followed by

proper intervention and treatment can improve the outcome. One drawback of the study was small sample size. Large prospective studies, therefore, are required to determine whether cTnI can be used as an independent mortality predictor and cost-effectiveness of estimating cTnI levels in these patients.

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