Serum Concentrations of Cardiac Troponin I Is Correlated With the Outcomes of Patients With Chronic Obstructive Pulmonary Disease Exacerbation Referred to Emergency Department

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Abstract- Acute exacerbations are the important reasons for hospitalization and death in chronic obstructive pulmonary disease (COPD) patients. We aimed to evaluate the relationship between serum concentrations of cardiac troponin I (cTnI) and the outcome of COPD patients visiting the emergency department with acute exacerbation of COPD (AECOPD). In this study, we included 90 AECOPD patients between October 2018 and October 2019. Serum cTnI was measured during the first 24 and 48 hours after admission. Patients were categorized into two groups positive cTnI values (≥0.3 ng/dl) and negative cTnI (<0.3 ng/dl). The outcomes of patients were compared between the two groups. Patients in Positive cTnI group in the first 24 hours and 48 hours compared to patients in negative group had significantly higher rate of in-hospital [(66.7% vs. 3.7%, *P*<0.001) and (50.0% vs. 3.8%, *P*<0.001), respectively)] and 30-day mortality rates [(88.9% vs. 3.3%, *P*<0.001) and (66.7% vs. 5.1%, *P*<0.001), respectively)]. The number of cases requiring intubation [(100% vs. 12.3%, *P*<0.001) and (75.0% vs. 12.8%, *P*<0.001), respectively)] and cardiopulmonary resuscitation (CPR) [(100.0% vs. 5.5%, *P*<0.05) and (100.0% vs. 5.5%, *P*<0.001), respectively)] as well as the duration of intensive care unit (ICU) stay [(37.00±14.61 vs 9.83±4.93 days, *P*<0.001) and (37.00±14.61 vs 9.83±4.93 days, *P*<0.001), respectively)] were also higher in cTnI positive patients. Increased cTnI during AECOPD is associated with higher rates of CPR, need for mechanical ventilation and in-hospital, short-term mortalities, and a longer ICU stay.

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Keywords: Cardiac troponin I; Chronic obstructive pulmonary disease; Exacerbation; Emergency

Introduction

Chronic obstructive pulmonary disease (COPD), a multifaceted respiratory condition, is a major cause of morbidity and mortality in the adult population worldwide (1). Comorbidities are common in COPD and expressively influence subjects' life quality, frequency of exacerbation, and survivance (2). Acute exacerbation of COPD (AECOPD) requiring hospitalization is correlated with a higher socioeconomic burden, increased refers to emergency hospital admission, and a six-percent risk of in-hospital mortality, making exacerbation prevention the crucial objective in COPD treatment (3,4). Re-admissions of COPD patients hospitalized for AECOPD are common and happen in about 60% of patients in the first year (5).

Smoking is an essential risk factor in COPD, and most COPD patients are current or former smokers

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(6,7). Therefore, these patients have a higher risk of emerging other smoking-correlated disorders, comprising ischemic heart disease (8,9). Concomitant cardiovascular diseases are increased in COPD patients and are associated with increased mortality (10). Cardiac troponins are specific markers of myocardial injury and are used universally for the diagnosis of myocardial infarction (MI) (11). Evaluation of cardiac-specific troponins (cardiac troponin T and troponin I (cTnT, cTnI)) is integrated with the diagnosis of acute MI (12).

The prevalence of raised troponin concentration in AECOPD is high, fluctuating from 18% up to 74% (13). Raised troponin concentration often specifies the presence of cardiac damage in AECOPD patients, associated with poor prognoses in patients (13,14). This is a vital and debatable concern since cardiovascular comorbidities deteriorate the COPD exacerbation outcome (15).

Several studies have been designed to define whether elevation of cardiac troponin during AECOPD could differentiate patients at higher mortality risk (13,16-20). However, the results were inconsistent, and the predictive value of this elevation in AECOPD in Emergency settings is still uncertain. Accordingly, in this study, we aim to evaluate the relationship between serum levels of cTnI and the outcome of COPD patients visiting the emergency room with acute exacerbation.

Materials and Methods

In this cross-sectional study, 134 consecutive COPD patients with AECOPD admitted to the emergency rooms of Imam Reza and Sina hospitals of Tabriz University of Medical Sciences were included between October 2018 and October 2019. The diagnosis was performed by the admitting specialist physicians, and then patients were screened for enrollment into the study a while after admission by the on-call investigator. Patients under 40 years old, with neuromuscular disease, renal failure, concomitant cancers, sepsis, pulmonary thromboembolism, cardiopulmonary arrest before admission, unstable hemodynamic state, more than 12 hours from emergency toward admission, and those unable to give informed consent were excluded. Finally, 90 AECOPD patients who satisfied all criteria were involved in the study. This study was directed according to the modified Declaration of Helsinki.

On admission, a comprehensive medical history was documented, and an examination was completed. Patients' baseline demographic (age, sex), weight, height, body mass index (BMI), hemodynamic, imaging, and laboratory findings were recorded. Patients were also followed for 30 days after discharge and in-hospital, and short-term mortality was recorded. The serum concentration of cTnI was measured during the first 24 h and 48h of admission, and patients were divided into two groups of positives (cTnI≥0.3 ng/dl) and negative cTnI (cTnI<0.3 ng/dl). cTnI was measured with the Electrochemiluminescence method using Cobas e 411 (Japan) and reported in ng/dl.

Outcomes

The primary outcomes were in-hospital mortality, the need for an Intensive Care Unit (ICU) stay, and its duration. Secondary outcomes were the rate of mechanical ventilation and cardiopulmonary resuscitation (CPR).

Statistical analysis

All data were analyzed using IBM SPSS software (version 20; SPSS Inc., Chicago, IL). Kolmogorov-Smirnov and Shapiro-Wilks tests were used to assess the normal distribution of data. Baseline characteristics are described by means of descriptive statistics (means and standard deviations [SD] or percentages). Group-wise comparisons were performed with the *Chi*-square test, Fischer's exact test, t-test, and Mann-Whitney U as appropriate. Results of the regression are presented as odds ratios (OR), with 95% confidence intervals (CI). Two-sided $P<0.05$ was considered statistically significant.

Results

Of 90 patients with COPD exacerbation, 50 (55.6%) were male and 40 (44.4%) female. Mean cTnI after 24 and 48 hours was 0.29±0.06 ng/dl (0.1-4.03) and 0.31±0.06 ng/dl (0.1-4.3) respectively. There were no significant differences between the two groups with positive and negative cTnI after 24 hours and 48 hours concerning demographic and clinical characteristics (all $P>0.05$) except O2sat (%) during the first 24 hours, which was significantly lower in positive cTnI participants in comparison with negative cTnI participants (76.44±7.16 vs. 82.16±7.54, $P=0.03$). Data are presented in Table 1.

Table 1. Demographic and clinical characteristics of study participants (n=90)

Variable		cTnI through the first 24 hours		cTnI through the first 48 hours	
		≥0.3 ng/dl (n=9)	<0.3 ng/dl (n=81)	≥0.3 ng/dl (n=11)	<0.3 ng/dl (n=79)
Age (yrs)		75.08±7.64	71.51±10.56	72.61±4.05	74.01±8.91
Weight (kg)		74.16±9.19	78.11±6.52	73.53±7.88	79.04±10.04
Height (cm)		169.77±5.73	170.37±6.97	165.36±5.73	169.54±8.43
BMI (kg/m^2)		25.63±2.56	27.42±4.94	26.16±3.74	28.64±3.06
Chronic illness	**DM**	3 (33.3%)	16 (19.8%)	4 (33.3%)	15 (19.2%)
	HTN	6 (66.7%)	55 (67.9%)	8 (66.7%)	53 (67.9%)
	CHF	1 (11.1%)	9 (11.1%)	1 (8.3%)	9 (11.5%)
	MI	1 (11.1%)	12 (14.8%)	1 (8.3%)	12 (15.4%)
Current smoker, n (%)		5 (55.5%)	47 (58.0%)	6 (50.0%)	46 (59.0%)
Alcohol		0 (0.00%)	2 (2.5%)	0 (0.00%)	2 (2.6%)
Opioid		2 (22.2%)	8 (9.9%)	2 (16.7%)	8 (10.3%)
Bakery		3 (33.3%)	23 (28.4%)	4 (33.3%)	22 (28.2%)
Drug	**serotide**	5 (62.5%)	46 (57.5%)	6 (54.5%)	45 (58.4%)
	atrovent	5 (62.5%)	48 (60%)	6 (54.5%)	47 (61%)
	salbutamol	5 (62.5%)	58 (72.5%)	7 (63.6%)	56 (72.7%)
	montelukast	0	3 (3.8%)	0	3 (3.9%)
	prednisolone	0	3 (3.8%)	0	3 (3.9%)
	beclomethasone	0	1 (1.3%)	0	1 (1.3%)
	N-acetylcysteine	0	2 (2.5%)	0	2 (2.6%)
	Ipratropium bromide	0	9 (11.1%)	1 (11.1%)	8 (10.4%)
	Fluticasone	0	2 (2.5%)	0	2 (2.6%)
Chief complaint	**Dyspnea**	88.9%	100%	11 (91.7%)	78 (100%)
	Cough with spectrum	88.9%	97.5%	11 (91.7%)	76 (97.4%)
	Fever	11.1%	18.5%	2 (16.7%)	14 (17.9%)
	Nausea and vomiting	11.1%	6.2%	1 (8.3%)	5 (6.4%)
Vital sign	**BP (mm/hg)**	136.33±19	130.88±13.9	135.58±18.52	130.79±13.78
	HR (beats/minute)	100.33±31.5	93.12±14.19	100.33±28.98	92.84±13.79
	RR (breaths /minute)	20.33±5.61	20.4±3.3	20±4.48	20.46±3.34
	BT(˚C)	31.18±0.5	37.06±0.41	37.22±0.53	37.05±0.41
	O2sat (%)	76.44±7.16	82.16±7.54	79.16±7.89	81.96±7.6

Data presented are mean±sd or frequency (percent). BMI: body mass index; cTnI: cardiac troponin I; DM: diabetes mellitus; HTN: hypertension; CHF: cardiac heart failure; MI: myocardial infarction; BP: blood pressure; HR: heart rate; RR: respiratory rate; BT: body temperature

Chest X-Ray (CXR), electrocardiogram (EKG), laboratory, and echocardiography findings of participants with positive and negative cTnI after 24 hours and 48 hours are shown in Table 2. As seen, there were significant differences concerning EKG and laboratory findings between the two groups with positive and negative cTnI after 24 hours and 48 hours. Right bundle branch block (RBBB) (44.4% vs. 17.3%, *P*=0.01) and ST elevation (22.2% vs. 2.5%, *P*=0.02) after 24 hours were more frequent in participants with positive cTnI in comparison with negative cTnI participants. The white blood cell (WBC) count (*P*=0.007 and *P*=0.006, respectively) and serum urea concentration (*P*=0.007 and *P*=0.03, respectively) after 24 hours and 48 hours were significantly higher in participants with positive cTnI in comparison with negative cTnI participants.

Table 3 shows the hospitalization inward and ICU and also in hospital and during 30-day mortality rates of study participants. Totally, 89 patients (98.9%) were admitted to the pulmonary ward, and 18 patients (20%) needed ICU care. The mean hospitalization duration inward was 8.05±6.24 days (3-35 days), and the mean hospitalization duration in ICU was 19.5±15.52 days (5-54 days). Twenty-four patients (26.7%) underwent spirometry, 2 (2.2%) underwent angiography and 60 patients (66.7%) underwent echocardiography. CXR was abnormal in 63 patients (70%).

Logistic regression was used to predict the risk of in-hospital and during 30-days mortalities. In-hospital mortality rate was increased in patients with positive cTnI after 24 hours (*P*<0.001, odds ratio (OR)=154.00, 95% CI=15.30-1550.04) and positive cTnI after 48 hours (*P*<0.001, OR=37.00, 95% CI=7.72-177.16). Also, during 30 days mortality rate was increased in patients with positive cTnI after 24 hours (p<0.001, OR=52.00, 95% CI=8.57-315.49) and positive cTnI after 48 hours (*P*<0.001, OR=25.00, 95% CI=4.96-125.85).

Logistic regression was used to predict the risks of CPR and intubation, which were increased in patients with positive cTnI after 48 hours [(*P*<0.001, OR=43.80, 95% CI=8.93-214.79) and (*P*<0.001, OR=20.40, 95% CI=4.71-88.33), respectively].

The reason for the lower ward stay in the patients with positive cTnI after 24 hours is due to the faster transfer to the ICU.

Patients who need intubation in patients with positive cTnI after 24 hours (100% vs. 12.3%, *P*=0.001) and positive cTnI after 48 hours (75% vs. 12.7%, *P*=0.001) were significantly higher than cTnI negative patients.

Table 2. Electrocardiogram, ST change, echocardiography, chest X-ray, and laboratory characteristics of study participants (n=90)

Variable		cTnI after the first 24 hours		*P**	cTnI after 48 hours		*P**
		≥0.3 ng/dl (n=9)	<0.3 ng/dl (n=81)		≥0.3 ng/dl (n=11)	<0.3 ng/dl (n=79)	
EKG	NSR, n (%)	4 (44.4%)	51 (63%)	0.52	4 (33.3%)	51 (65.4%)	0.12
	RBBB, n (%)	4 (44.4%)	14 (17.3%)	0.01	6 (50%)	12 (15.4%)	0.04
	LBBB, n (%)	1 (11.1%)	6 (7.4%)	0.4	1 (8.3%)	6 (7.7%)	0.23
	AF, n (%)	0	7 (8.6%)	-	1 (8.3%)	6 (7.7%)	0.53
	RBBB+AF, n (%)	0	3 (3.7%)	-	0	3 (3.8%)	-
ST change	ST elevation, n (%)	2 (22.2%)	2 (2.5%)	0.02	2 (16.7%)	9 (11.5%)	0.34
	ST depression, n (%)	0	2 (2.5%)	-	3 (25%)	8 (10.3%)	0.21
	No changes, n (%)	7 (77.8%)	77 (95.1%)	0.04	7 (58.3%)	61 (78.2%)	0.09
Echocardiography	EF (%)	45±10	47.92±8.47	0.46	45±10	47.62±8.47	0.46
	MR, n (%)	2 (40%)	42 (76.4%)	0.11	5 (62.5%)	39 (75%)	0.36
	TR, n (%)	0	41 (74.5%)	-	3 (37.5%)	38 (73.1%)	0.06
	AR, n (%)	1 (20%)	11 (20%)	0.7	3 (37.5%)	9 (17.3%)	0.19
	PHTN, n (%)	0	2 (3.6%)	-	0	2 (3.8%)	-
	AS, n (%)	0	1 (1.8%)	-	0	1 (1.9%)	-
	MS, n (%)	0	1 (1.8%)	-	0	1 (1.9%)	-
CXR	Hyperlucency, n (%)	3 (33.3%)	43 (53.1%)	0.22	4 (33.3%)	42 (53.8%)	0.15
	PE, n (%)	0	12 (14.8%)	-	1 (8.3%)	11 (14.1%)	0.49
	Consolidation, n (%)	4 (44.4%)	34 (43%)	0.57	5 (41.7%)	33 (42.3%)	0.61
	Pneumothorax,n (%)	0	1 (1.2%)	-	0	1 (1.3%)	-
	Atelectasis, n (%)	0	1 (1.2%)	-	0	1 (1.3%)	-
Laboratory	WBC count (u/ml)	13.4±7.58	9.1±3.80	0.007	12.8±7.60	9.1±3.57	0.006
	Hemoglobin (g/dl)	15.3±3.34	14.32±2.56	0.29	14.2±3.56	14.45±2.5	0.76
	Urea (mg/dL)	85.11±76.01	50.83±28.12	0.007	75.5±68.23	50.99±28.29	0.03
	Creatinine (mg/dl)	1.44±0.94	1.2±0.6	0.29	1.44±0.86	1.19±0.6	0.21
	Na (mmol/L)	139.33±5.17	140.04±2.97	0.53	139.58±4.48	140.03±3.01	0.65
	K (mEq/L)	4.16±0.68	4.14±0.48	0.9	4.17±0.65	4.14±0.47	0.83
	PH	7.32±0.11	7.36±0.06	0.15	7.33±0.9	7.36±0.06	0.21
	$Hco3^-$ (mEq/L)	32.73±11.24	30.64±6.12	0.38	30.66±10.5	30.87±6.05	0.92
	PaCO2, (%)	62.47±13.06	53.43±13.78	0.06	58.33±14.32	53.72±13.84	0.87

Data presented are mean±sd or frequency (percent). *Chi-square test or Mann–Whitney U test or Independent samples *t*-Test. AF: Atrial fibrillation; AR: Aortic regurgitation; AS: Aortic stenosis; cTnI: Cardiac troponin I; EF: Ejection fraction; LBBB: Left bundle branch block; MR: Mitral regurgitation; MS: Mitral stenosis; NSR: Normal sinus rhythm; PaCO2: Arterial partial pressure of carbon dioxide; PE: Pulmonary embolism; PHTN: Pulmonary hypertension; RBBB: Right bundle branch block; TR: Tricuspid regurgitation; WBC: White blood cell

Table 3. Hospitalization and Mortality Rates of Study Participants (n=90)

	cTnI after the first 24 hours		
	≥0.3 ng/dl (n=9)	**<0.3 ng/dl (n=81)**	***P****
Hospitalization in ward (day)	3.37±2.66	8.51±6.31	0.002
Hospitalization in ICU (day)	37.00±14.61	9.83±4.93	<0.001
Intubation, n (%)	9 (100.0%)	10 (12.3%)	<0.001
CPR, n (%)	9 (100.0%)	5 (5.5%)	<0.001
Mortality in hospital, n (%)	6 (66.7%)	3 (3.7%)	<0.001
Mortality during 30 days, n (%)	8 (88.9%)	4 (3.3%)	<0.001
	cTnI after 48 hours		
	≥0.3 ng/dl (n=12)	**<0.3 ng/dl (n=78)**	***P****
Hospitalization in ward (day)	5.72±6.01	8.38±6.24	0.030
Hospitalization in ICU (day)	37.00±14.61	9.83±4.93	<0.001
Intubation, n (%)	9 (75.0%)	10 (12.8%)	<0.001
CPR, n (%)	9 (100.0%)	5 (5.5%)	<0.001
Mortality in hospital, n (%)	6 (50.0%)	3 (3.8%)	<0.001
Mortality during 30 days, n (%)	8 (66.7%)	4 (5.1%)	<0.001

Data presented are mean±sd or frequency (percent). *Chi-square test or Mann–Whitney U test. CPR: Cardiopulmonary resuscitation; cTnI: Cardiac troponin I; ICU: Intensive Care Unit

Discussion

In the present study, we compare the AECOPD patients admitted to the emergency departments based on serum concentration of cTnI after 24h and 48 h after admission regarding several demographic and clinical presentations and achieved interesting findings. RBBB and ST elevation were more prevalent in AECOPD patients with a cTnI concentration of 0.3 ng/dl and higher than in patients with a cTnI concentration of lower than 0.3 ng/dl during the first 24 hours. AECOPD patients with positive cTnI had higher WBC and urea concentrations. Additionally, lengths of ICU hospitalization and CPR, in-hospital mortality, and 30 days mortality rates were significantly higher in patients with positive cTnI in comparison with negative cTnI patients (after the first 24 and 48 hours).

There have been several studies available over the previous decade which have concentrated on the innovation and evaluation of AECOPD correlated biomarkers (21). Generally, plasma cTnI is one of the main measures in the diagnosis of MI (12). However, increased values of cTnI have been perceived in some other conditions, comprising left ventricular hypertrophy (LVH), chronic renal failure (CRF), diabetes, heart failure (HF), and pulmonary embolism (22,23). Preceding investigations have studied the prognostic role of cardiac biomarkers in AECOPD patients with inconsistent findings (16,17,20,24-27). The predictive value of the elevation of cardiac Tn has been debated in recent times. Baillard *et al*., (16) showed that elevated cTnI is an important and independent prognosticator of death in a prospective cohort study in two ICUs among 71 AECOPD patients. Brekke *et al*., (17) studied 897 patients discharged after COPD treatment and concluded that elevated cTnT was considerably correlated with increased all-cause mortality, with a hazard ratio (HR) of 1.64 (1.15-2.34). However, other prospective investigations were unsuccessful in correlating the elevated levels of cTnT with long-term mortality (20,28). Marcun *et al.*, reported cTnI level has no significant correlation with mortality but could predict the hospitalization duration (28).

Our results showed that ICU hospitalization length was significantly higher in cTnI positive patients, but ward hospitalization length was significantly lower in cTnI positive patients due to faster transfer to the ICU. Similar to our findings, several studies reported ICU hospitalization length was higher in cTnI-positive patients (24,29-31). However, Gupta *et al*., (32) showed that there was no relationship between cTnI and hospitalization length inward and ICU.

According to our findings, there were significant correlations between cTnI after 24h and 48 h of admission and patients' intubation. Patients with elevated cTnI were more likely to need intubation after 24h and 48 h of admission. The OR for intubation need in Patients with elevated cTnI after 48 h of admission was 20.4. Previous studies have shown that elevated cTnI correlated significantly with the need for noninvasive ventilatory support (19,29,32).

In AECOPD patients, Raji *et al*., (33) found that

cTnI level has not correlated with arterial blood gas (ABG) variables [PH, $HCO3^-$, arterial partial pressure of carbon dioxide ($PaCO_2$)]. Also, the results of the present study support that positive cTnI levels are not associated with ABG variables in patients with AECOPD. Harvey *et al*., (24) showed that in the presence of positive cTnI, PH was lower and $PaCO_2$ higher. Hasaneen *et al*., (30) reported that positive cTnI had a significant role in lower PH (PH=7.29 vs. PH=7.39). Baillard *et al*., (16) demonstrated $PaCO_2$was lower in AECOPD patients with positive cTnI.

The principal mechanism for cardiac troponin elevation throughout AECOPD is uncertain. It could be correlated to associated HF, or other issues, such as acute right ventricle dysfunction, which is prevalent in severe COPD (34,35). Another likely hypothesis is that several patients could have a quiet coronary artery disease (CAD), and cardiac Tn elevation may be an indicator of the disease development simplified by the AECOPD induced modifications in inflammation, endothelial dysfunction, and platelet reactivity (36,37).

To our knowledge, our study is the first to evaluate the prognostic value of cTnI in AECOPD patients in emergency settings. The other strength of this study is considering different confounders which may affect and/or restrain cardiac Tn elevation during AECOPD, such as age, creatinine, tachycardia and echocardiography, CXR and laboratory findings, past history of long-term oxygen therapy, and low hemoglobin levels (19,38,39).

Our findings crenelated previous results and proposed that cardiac Tn elevation at the time of emergency department admission of AECOPD is correlated with ICU hospitalization length and rates of intubation, CPR, and in-hospital and during 30-day mortality. It suggests that cTnI measurement could be considered a routine, simple and inexpensive measurement for risk stratification of AECOPD patients in emergency departments. Future studies are required to comprehend how to manage these patients and how to advance their outcomes.

Our study has several limitations which should be taken into account in the explanation of the findings. The main limitation of our study is the observational design. Secondly, we could not eliminate bias from other confounding factors that were not measured in our analysis.

In conclusion, the results of the present study showed that cTnI concentrations of 0.3 ng/dl and higher in AECOPD patients are correlated with the higher rates of in-hospital and 30-day mortality, the need for CPR, and mechanical ventilation support, and also the higher length of hospitalization in the ICU.

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