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FREQUENCY OF NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION IN PATIENTS PRESENTING WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is the most prevalent preventable lung disease and is defined as persistent airflow limitation due to chronic inflammation of the airways.

Objective: To determine the frequency of non-ST-segment elevation myocardial infarction (NSTEMI) in patients presenting with acute exacerbation of chronic obstructive pulmonary disease.

Methods: This study was a cross-sectional study carried out at Aga Khan University and Hospital, Karachi for six months after approval of synopsis. The subjects were patients with diagnosed COPD who were acutely exacerbating, who were non-probability consecutively sampled within the age range of 40–80 years, both male and female. Patients with a prior myocardial infarction were excluded, as well as those with interstitial lung disease, prior percutaneous coronary intervention or coronary artery bypass grafting (CABG), valvular heart disease, renal failure or anticoagulant use. Demographic and clinical information were collected. All patients had 12 lead ECG and serial serum Troponin I levels. NSTEMI was diagnosed on the basis of the absence of ST-segment elevation on the ECG and Troponin I ≥0.04 ng/mL on two occasions. SPSS 22 software was used for data analysis.

Results: The mean age was 66.95±9.126 years. There were 79 (62.2%) males and 48 (37.8%) females. Troponin I was positive in 45 (35.4%) patients. ECG abnormalities included ST-segment depression in 11 (8.7%) and T-wave inversion in 9 (7.1%). NSTEMI was present in 20 (15.7%) patients. ECG changes (p=0.01) and Troponin I positivity (p=0.001) were significantly associated with NSTEMI.

Conclusion: It was concluded from the study that patients having acute exacerbation of chronic obstructive pulmonary disease (AECOPD) are at a higher risk of developing non-ST-segment elevation myocardial infarction (NSTEMI).

KEYWORDS: Disease Exacerbation; Electrocardiography; Non-ST Elevated Myocardial Infarction; Pulmonary Disease, Chronic Obstructive.

INTRODUCTION

Non-ST-segment elevation myocardial infarction (NSTEMI) is a major type of acute coronary syndrome (ACS) which has no persistent ST-segment elevation on ECG but is associated with myocardial necrosis, which can be identified by elevated cardiac biomarkers. Current recommendations for the management of non-ST-segment elevation acute coronary syndromes include prompt identification, risk stratification, serial electrocardiogram evaluation, cardiac troponin measurement and prompt intervention, as delayed diagnosis may lead to a higher morbidity and mortality [1]. This is important especially in patients with chronic obstructive pulmonary disease (COPD) as acute respiratory symptoms can mask the cardiac symptoms and make the diagnosis of NSTEMI very difficult.

COPD is a chronic inflammatory airway disease, which is not only linked to respiratory disability but also significant cardiovascular comorbidity. COPD patients are burdened with the coronary artery disease and may suffer from unfavourable outcomes during hospitalization with myocardial infarction. In an analysis of the incidence and prognosis of cases of ST-elevation and non-ST-elevation myocardial infarction, matched for population, COPD was found to have an impact, demonstrating the close clinical relationship that exists between obstructive lung disease and acute coronary events [2]. This relationship is more significant in exacerbations of COPD, as during exacerbations of disease, hypoxaemia, tachycardia, systemic inflammation, sympathetic overactivity and haemodynamic stress leads to a greater myocardial oxygen demand, and a lower oxygen supply.

In recent years, it has been recognised that acute exacerbation of COPD is not just a lung deterioration, but a systemic event. It has been suggested that systemic inflammation from exacerbation of COPD or pneumonia in patients with COPD may be responsible for cardiac troponin elevation, implying myocardial injury in the course of acute respiratory illness [3]. Troponin elevation is not necessarily a type 1 myocardial infarction, but is clinically important as it signifies myocardial stress, occult coronary disease, demand ischaemia or true acute coronary syndrome. In addition, long-term cohort data indicate that cardiac biomarkers obtained during exacerbation of COPD are also linked to future outcomes, which indicates their prognostic value in this patient population [4].

There are several recent studies that have added more evidence that exacerbation of COPD is followed by a period of heightened cardiovascular vulnerability. A post hoc analysis of the IMPACT trial showed that there was a time-dependent increase in cardiovascular events after exacerbations of COPD, implying that the post-exacerbation period may been a high-risk period for acute cardiac events [5]. In a similar way, a systematic review and meta-analysis found an association between exacerbations of COPD and acute cardiovascular events, supporting the idea that exacerbations can precipitate and/or uncover clinically important cardiac disease [6]. These findings are significant for hospital practice as the patients who present with acute exacerbation of COPD often are treated as a pulmonary presentation and the NSTEMI may go underdiagnosed if not specifically sought.

In particular, cardiac troponin assessment has relevance in this setting. Troponin is also raised in hospitalised patients with exacerbation of COPD and has been linked to major adverse cardiac events as well as COPD readmission, indicating that myocardial injury during exacerbation has an adverse prognostic impact not only for the cardiovascular system but also for the lung [7]. There has also been an interest in other laboratory parameters that are readily available and may be of predictive value in the setting of acute exacerbation of COPD, where there is a need for simple tools to identify the highest risk patients on admission [8]. Yet, though there is growing evidence that cardiac risk is high following exacerbation of COPD, the true incidence of NSTEMI may not be well characterized in many clinical settings.

The cardiovascular risk of exacerbations of COPD has also been confirmed in large real-world cohort studies. The EXACOS-CV cohort from the Netherlands demonstrated cardiovascular event risk during COPD exacerbation, suggesting this risk association is detectable in real-world healthcare data, not just trial cohorts [9]. Additionally, a nationwide population-based cohort study demonstrated that exacerbations were able to predict severe cardiovascular events in patients with COPD and stable cardiovascular disease, lending further evidence to exacerbations serving as triggers for major cardiovascular events in vulnerable patients [10].

So, there is a strong rationale for the current study. Acute exacerbation of COPD can provide a physiological basis for the development of NSTEMI, but the diagnosis might be missed as dyspnoea, chest tightness, tachycardia and hypoxaemia may be mistaken as being due to the respiratory disease alone. The identification of the frequency of NSTEMI among patients presenting with acute exacerbation of COPD is clinically important as it could be used to increase early detection and direct proper cardiac assessment, prompt timely treatment, decrease missed myocardial infarction, and identify a high-risk group of patients that could benefit from more intensive follow-up. Therefore, this study could provide some locally valuable information to help to improve diagnostic procedures and integrated cardiopulmonary treatment in patients with acute exacerbation of COPD.

METHODS

This cross-sectional study was performed at Aga Khan University and Hospital, Karachi. The study period was of 6 months after getting approval from CPSP. A non-probability consecutive sampling technique was used. The sample size was determined with OpenEpi with an 5% margin of error, 70% expected positive Troponin I as reported with previous studies [10], and 95% confidence interval. A sample size of **127 patients** was calculated.

Patients of both gender aged 40–80 years with already diagnosed chronic obstructive pulmonary disease (COPD) presenting with symptoms of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) were included. Acute exacerbation of chronic obstructive pulmonary disease (COPD) was defined based on an increase in dyspnoea it was labelled positive when the patient became uncomfortable with breathing after walking 10 steps, and combined with cough, increased sputum production and change in sputum colour from mucoid to purulent in the previous 1 week. Patients who had previously diagnosed myocardial infarction, interstitial lung disease, preceding percutaneous coronary intervention or coronary artery bypass grafting, valvular heart disease, acute or chronic renal failure and using anticoagulant drugs were excluded. History was taken at the time of admission and exclusion criteria were identified.

After written informed consent was obtained, all eligible patients were enrolled in the study. Demographic and clinical data such as age, sex, weight, height, BMI and duration of COPD exacerbation was captured on a predesigned proforma.

All patients with acute exacerbation of chronic obstructive pulmonary disease underwent a 12-lead electrocardiogram. ST segment changes were found and recorded. Non-ST-segment elevation myocardial infarction was diagnosed by the presence of serum Troponin I level $\geq$ 0.04ng/mL on two occasions without ST elevation on electrocardiogram. ST-segment elevation was evaluated in the following leads: leads II, III and aVF for inferior wall myocardial infarction, leads V1-V6 for anterior wall myocardial infarction and leads I and aVL for lateral wall myocardial infarction.

All the patients enrolled were subjected to blood sampling and the blood sent to the hospital laboratory for cardiac Troponin I measurement. The standard kit for Troponin I Assay in the laboratory was used. Cardiac Troponin I level > 0.04 ng/mL was taken as a positive result for myocardial infarction. Additional studies were conducted using echocardiography to evaluate the presence of cardiac dysfunction.

Data was analysed in SPSS version 22. Continuous (quantitative) variables such as age, weight, height, body mass index, duration of chronic obstructive pulmonary disease exacerbation, and Troponin I value, were presented as mean and standard deviation. Qualitative variables (gender, presence of ST-segment changes) were represented as frequency and percentage. Stratification was used to determine the effect of the effect modifiers such as gender, age, weight and height (BMI), and duration of exacerbation of chronic obstructive pulmonary disease (COPD). After stratification, the chi-square test was used and the P value of ≤0.05 was considered statistically significant.

RESULTS

A total of 127 patients with acute exacerbation of chronic obstructive pulmonary disease were included in the study. The mean age was 66.95±9.126 years, mean height was 164.38±3.021 cm, mean weight was 65.71±9.121 kg, mean duration of symptoms was 4.10±1.578 days, mean BMI was 24.29±3.153 kg/m², and mean Troponin I level was 0.17±0.431 ng/mL (**Table 1).**

Table 1: Descriptive statistics of continuous variables among patients with acute exacerbation of COPD (n=127)

Variable	Minimum	Maximum	Mean ± SD
Age (years)	42	80	66.95±9.126
Height (cm)	158	169	164.38±3.021
Weight (kg)	45	95	65.71±9.121
Duration of symptoms (days)	1	8	4.10±1.578
BMI (kg/m²)	17.6	35.2	24.29±3.153
Troponin I (ng/mL)	0.005	2.491	0.17±0.431

Of the 127 patients, 79 (62.2%) were male and 48 (37.8%) were female. Most patients belonged to the 61–70 years and 71–80 years age groups (38.6% each). Duration of symptoms was 1–4 days in 63.8% patients, while 59.1% had normal BMI (**Table 2**).

Table 2: Distribution of demographic and clinical characteristics among patients with acute exacerbation of COPD (n=127)

Variable	n (%)
Gender	
Male	79 (62.2)
Female	48 (37.8)
Age group (years)	
40–50	8 (6.3)
51–60	21 (16.5)
61–70	49 (38.6)
71–80	49 (38.6)
Duration of symptoms	
1–4 days	81 (63.8)
5–8 days	46 (36.2)
BMI category	
Underweight	4 (3.1)
Normal weight	75 (59.1)
Overweight	44 (34.6)
Obesity	4 (3.1)

Normal ECG findings were observed in 107 (84.3%) patients, while ST-segment depression and T-wave inversion were present in 11 (8.7%) and 9 (7.1%) patients, respectively. Troponin I was positive in 45 (35.4%) patients. NSTEMI was diagnosed in 20 (15.7%) patients (**Table 3).**

Table 3: Distribution of ECG changes, Troponin I and NSTEMI among patients with acute exacerbation of COPD (n=127)

Variable	n (%)
ECG changes	
Normal	107 (84.3)
ST-segment depression	11 (8.7)
T-wave inversion	9 (7.1)
Troponin I	
Positive (>0.04 ng/mL)	45 (35.4)
Negative (<0.04 ng/mL)	82 (64.6)
NSTEMI in COPD	
Present	20 (15.7)

Absent	107 (84.3)

Stratification analysis showed no significant association of NSTEMI with gender (p=0.469), age group (p=0.442), duration of symptoms (p=0.373), or BMI category (p=0.730). However, ECG changes (p=0.01) and Troponin I positivity (p=0.001) were significantly associated with NSTEMI (**Table 4**).

Table 4: Stratification of NSTEMI among patients with acute exacerbation of COPD (n=127)

Variable	NSTEMI Present n (%)	NSTEMI Absent n (%)	Total n (%)	Chi-square	P-value
Gender				0.529	0.469
Male	11 (13.9)	68 (86.1)	79 (100.0)		
Female	9 (18.8)	39 (81.2)	48 (100.0)		
Age group (years)				2.692	0.442
41–50	2 (25.0)	6 (75.0)	8 (100.0)		
51–60	1 (4.8)	20 (95.2)	21 (100.0)		
61–70	8 (16.3)	41 (83.7)	49 (100.0)		
71–80	9 (18.4)	40 (81.6)	49 (100.0)		
Duration of symptoms				0.792	0.373
1–4 days	11 (13.6)	70 (86.4)	81 (100.0)		
5–8 days	9 (19.6)	37 (80.4)	46 (100.0)		
BMI category				1.296	0.730
Underweight	1 (25.0)	3 (75.0)	4 (100.0)		
Normal weight	13 (17.3)	62 (82.7)	75 (100.0)		
Overweight	5 (11.4)	39 (88.6)	44 (100.0)		
Obesity	1 (25.0)	3 (75.0)	4 (100.0)		
ECG changes				127.0	0.01
Normal	0 (0.0)	107 (100.0)	107 (100.0)		
ST-segment depression	11 (100.0)	0 (0.0)	11 (100.0)		
T-wave inversion	9 (100.0)	0 (0.0)	9 (100.0)		
Troponin I				43.256	0.001
Positive	20 (44.4)	25 (55.6)	45 (100.0)		
Negative	0 (0.0)	82 (100.0)	82 (100.0)		

DISCUSSION

In the current study, 20 (15.7%) of 127 patients with acute exacerbation of chronic obstructive pulmonary disease were noted to have NSTEMI. Forty-five (35.4%) and 20 (15.7%) patients had a positive troponin I and abnormal ECG, respectively, with 11 (8.7%) having an ECG with ST-segment depression and 9 (7.1%) with T-wave inversion. These results suggest that there is a clinically significant number of patients with acute exacerbation of COPD who have myocardial injury or NSTEMI at the time of presentation. This is pertinent as recent population-based evidence has demonstrated that nonfatal cardiovascular events are more likely to occur post-COPD exacerbation, especially in early post-exacerbation phase [11].

Results of the present study support evidence that exacerbation of COPD is not only a pulmonary event, but also a time of heightened cardiovascular risk. Daniels et al. [12] reported that there were increased risks of death and cardiovascular events after COPD exacerbation, indicating the need for active cardiovascular assessment in patients hospitalized with acute respiratory deterioration. Indeed, cardiovascular events were found following COPD exacerbations in a large real-world Italian cohort, further supporting the cardiopulmonary interaction found in patients with COPD [13]. This concept is reinforced in the current study as NSTEMI was diagnosed in 15.7% of patients and the significance of not assigning all breathless and chest discomfort to pulmonary disease is emphasised.

The strong relationship of ECG changes with NSTEMI in this study also has clinical implications. ST segment depression and T wave inversion were more likely to be classified as NSTEMI while no patient with a normal ECG finding had an NSTEMI. This finding is similar to the general results that COPD exacerbations have cardiopulmonary impact and are linked to cardiac risk in other populations [14]. The authors Hawkins et al. also showed increased long-term cardiovascular risk following an exacerbation of COPD, indicating that cardiac monitoring during and after an exacerbation may be useful to identify patients at risk of poor cardiac outcome [15].

In the current study, troponin I is a significant parameter associated with NSTEMI. The proportion of all 20 patients with NSTEMI had a positive Troponin I and 25 patients had positive Troponin I without meeting the study criteria for NSTEMI. This means that when the troponin is raised in AEC of COPD, it can be a spectrum of myocardial injury up to definite myocardial infarction. The clinical significance of cardiac involvement in exacerbation episodes was demonstrated by Matsunaga et al. who reported a higher risk of severe cardiovascular

events after COPD exacerbations in Japan [16]. In the same manner, Yang et al. showed that COPD exacerbation is a risk factor for future cardiovascular events in a longitudinal study, which suggests that cardiac injury due to exacerbation cannot be overlooked [17].
The present study did not find statistically significant association of NSTEMI with gender, age group, duration of symptoms and BMI. This indicates that NSTEMI can occur in various demographic and clinical sub-group of patients with acute exacerbation of COPD. Thus, screening should not be restricted to the older patients, males or patients with longer symptom duration. Cockell et al. also stressed the possible prognostic significance of raised troponin in clinically suspected coronary events in severe COPD exacerbation, and advocated routine consideration of cardiac biomarkers in such cases [18].
In the present study, 35.4% of patients had positive Troponin I while the NSTEMI was confirmed in 15.7%. This distinction is clinically relevant as this increase in troponin during a COPD exacerbation can be due to demand ischaemia, hypoxaemia, tachycardia, systemic inflammation or to coronary artery disease. Morgan et al. reported that acute coronary syndrome occurs in hospitalised adults following infective exacerbation of COPD, which strengthens the argument that exacerbation of COPD can lead to or uncover the acute coronary pathology [19]. Recent data have also demonstrated that there is an increased long-term cardiovascular risk with severe exacerbations of COPD [20] adding to the argument for an integrated cardiopulmonary assessment in the COPD population.
The study solved an important clinical problem in a high-risk population of those with acute exacerbation of COPD. NSTEMI was clearly defined with an operational criterion which included ECG findings and serial Troponin I levels. Various clinical and demographic parameters were also assessed in the study, such as the duration of the symptoms, ECG changes, Troponin I status, gender, and BMI, which helped in determining the possible association with NSTEMI. The patient with acute exacerbation of COPD should be carefully evaluated for the potential cardiac complication, particularly if there are ECG changes or elevated levels of Troponin I. Routine ECG and troponin I should be considered in patients with COPD who are admitted with an acute exacerbation of their disease, especially if accompanied by severe dyspnoea, chest discomfort, hypoxaemia and cardiovascular risk factors. The need for larger multicentre studies with follow-up to evaluate the prognostic value of NSTEMI and troponin elevation in COPD exacerbation is felt. Future studies should also consider echocardiographic results, coronary imaging if possible and long-term cardiovascular outcome to further distinguish myocardial injury from definite ACS.

Limitations of study: This is a single centre cross sectional study with relatively small number of patients, which may limit generalisability of the results. Non-probability consecutive sampling was employed in the study and this might be a source of selection bias. Long-term outcomes, such as mortality, readmission and future cardiovascular events, were not measured. Coronary angiography was not performed to confirm coronary artery obstruction and differentiation between type 1 myocardial infarction, type 2 myocardial infarction and non-ischaemic myocardial injury was not possible.

CONCLUSION

Finally, clinically significant number of patients with acute exacerbation of COPD had NSTEMI. Troponin I positivity was more common than confirmed NSTEMI, and the positivity of troponin I in AECOPD must therefore be interpreted with caution, as it can be due to myocardial injury or a type II myocardial infarction. In this cohort ECG changes in the form of ST-segment depression and T-wave inversion favoured the diagnosis of NSTEMI. Patients who may need more cardiac assessment may be identified by routine ECG assessment and serial troponin measurement.

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