

# Impact of Comorbid Ischemic Heart Disease on Short-Term Outcomes of Patients Hospitalized for Acute Exacerbations of COPD

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**Background:** Ischemic heart disease (IHD) is a leading cause of mortality and morbidity in patients with COPD. The contribution of IHD to acute outcomes in patients with acute exacerbation of COPD (AECOPD) is not known in detail. The present study assessed the effect of comorbid IHD on length of stay (LOS), risk of intensive care unit (ICU) admission and death as indicators of the short-term outcomes for patients hospitalized for AECOPD.

**Materials and Methods:** Medical records of patients hospitalized for AECOPD from September 2008 to March 2014 were reviewed. Data extracted from patient records regarding the presence of comorbidities and the markers of disease severity were analyzed using logistic regression for ICU admission and mortality, the Kaplan-Meier method, log rank test and Cox regression for LOS.

**Results:** Of 507 separate admissions, 146 episodes (28.8%) occurred in patients with IHD. The median LOS was 7 days [interquartile range (IQR) 6, 11] in patients with IHD versus 6 days (IQR 5, 8) for patients without IHD. After adjustment for confounders, LOS was found to be 26% longer ( $p=0.033$ ) for patients with IHD. The adjusted odds ratio for the risk of ICU admission and death in patients with IHD was 2.97 and 3.86, respectively.

**Conclusion:** Patients hospitalized for AECOPD with comorbid IHD had longer LOS, greater risk for ICU admission and death. It seems that this group is a particular COPD subtype with a more severe degree of COPD and poorer acute outcomes that may influence optimal management.

**Key words:** Chronic Obstructive Pulmonary Disease; Comorbidity; Myocardial Ischemia

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide (1). It affects more than 5% of the population (2). As a result of its high incidence and chronicity, COPD results in frequent hospitalizations for acute exacerbations, high resource utilization with numerous physician visits, and the need for chronic therapy (3). Comorbidities may diminish survival rates in patients with COPD, are often under-recognized and under-treated and can frequently result in

death independent of respiratory failure (4-7). Considerable research has been undertaken and clinical interest exists about the extra-pulmonary manifestations and comorbid conditions related to COPD. The extent to which comorbidities contribute to COPD severity has not yet been well realized (8). Cardiovascular, musculoskeletal and psychological conditions are among the most prevalent comorbidities. In particular, IHD is a major cause of mortality and morbidity in the COPD population as a whole (9).

Ischemic heart disease and its complications (myocardial infarction, heart failure, arrhythmia) are common in patients with COPD and may be more prevalent than predicted for shared risk factors such as smoking and aging (10,11). These could be linked to systemic inflammation (12). The presence of IHD may help predict survival and hospitalization (8).

Exacerbations of COPD are defined as episodes of increased dyspnea and cough and changes in the amount and character of sputum (1). The COPD exacerbations leading to hospitalization are associated with high morbidity and mortality. The contribution of specific comorbidities to short-term outcomes has not yet been well realized; existing researches have used either small clinical cohorts or administrative data and have reported conflicting outcomes. Recognition of co-existent diseases that could influence the results provides chances to address these conditions proactively and develop overall COPD care (13).

The present study assessed the effect of comorbid IHD on the duration of hospitalization, risk of ICU admission and death as indicators of the outcome of hospital care among patients admitted for AECOPD.

## **MATERIALS AND METHODS**

This historical cohort study was based on the analysis of medical records of patients admitted to a large tertiary hospital from September 2008 to March 2014 for AECOPD. Data were extracted from the medical records by one reviewer and entered into an Excel spreadsheet. The study was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences.

The study population comprised patients aged  $\geq 50$  years with smoking history of more than 10 packs/year who were admitted for AECOPD under the care of the respiratory medicine team at the Imam Hospital in the city of Sari, Iran. These patients were identified by reviewing the available medical records of all admitted patients whose attending physician was a respiratory subspecialist. The patients were diagnosed according to the international classification of diseases code J41–J44; IHD was defined as stable angina pectoris, unstable angina pectoris, previous

MI, and previous coronary artery intervention such as angioplasty, stenting and bypass grafting.

Patients with pneumonia, bronchiectasis, pulmonary thromboembolism, obstructive sleep apnea/hypopnea syndrome and intrathoracic malignancies were excluded from the study.

The length of hospital stay was ascertained from the records of admission and discharge dates. The study included all admissions for each patient within the intended study period.

Primarily, a statistical descriptive analysis of crude data was performed. Continuous data were demonstrated as mean and standard deviation (SD). In order to express numerical variables with non-normal distribution, their median and IQR (25<sup>th</sup> percentile, 75<sup>th</sup> percentile) were used. Frequency and percentage for categorical variables were used to express the results. To assess the normality of the numerical variables, the Kolmogorov-Smirnov test was used.

To analyze the differences of quantitative variables between groups, the student t-test and the Mann-Whitney U test were used for variables with normal and non-normal distributions, respectively. The Pearson's chi-squared test was used to study the relationship between qualitative variables. The Kaplan-Meier method and log rank test were used to compare LOS between patients with and without IHD.

Subjects with and without IHD were compared to assess the association between outcomes and IHD while adjusting for patient's age, gender, tobacco use (packs/year) and presence of hypertension (HTN) and diabetes mellitus (DM) as comorbidities and the use of home oxygen, admission arterial blood gas pH and requiring non-invasive mechanical ventilation as markers of disease severity using logistic regression for ICU admission and mortality and Cox regression for LOS.

The data were analyzed using SPSS version 21.0 software (Microsoft, IL, USA).  $P < 0.05$  was considered statistically significant and variables at  $P < 0.3$  for univariate logistic regression and Cox regression analyses were used as covariates in multivariate logistic regression and Cox regression analyses.

## RESULTS

During the study period, there were 736 separate admissions for patients having a final diagnosis of AECOPD. Among them, 664 had charts available for review. An additional 157 episodes were excluded when their medical records indicated that the main reason for admission was not AECOPD. Most of these patients had pneumonia. Data were ultimately collected for 507 admissions (68.8% of the original sample). A total of 146 episodes (28.8%) occurred in patients with IHD having a mean age of 66.91 ± 11.26 versus 68.57±11.51 years for patients without IHD.

The demographic and clinical characteristics of 507 patients with AECOPD are shown in Table 1 and indicate that there was no significant difference for age or gender distribution, tobacco use (packs/year), disease duration, cholesterol and left ventricular ejection fraction (LVEF) between patients with and without IHD. There were higher rates of comorbidities (DM, HTN and dyslipidemia) in patients with IHD compared to patients without IHD as shown in Figure 1.

**Table 1.** Demographic and clinical characteristics of patients with AECOPD with and without comorbid IHD

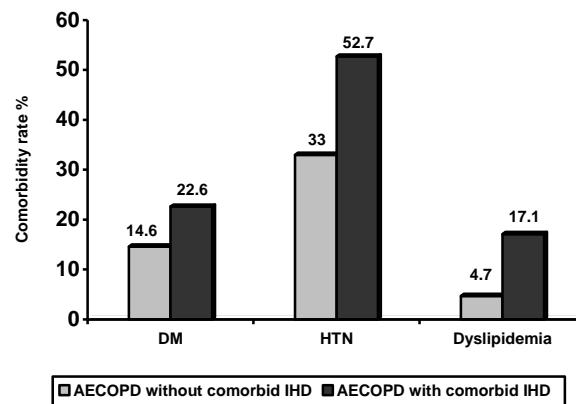
	AECOPD without IHD† (n = 361)	AECOPD with IHD‡ (n = 146)	P-value† vs. ‡
Age, year	68.57 (11.51)	66.91 (11.26)	0.17
Male sex, n (%)	289 (80%)	117 (80.1%)	0.97
Smoking, packs/year	20 (13, 53)	20 (15, 55)	0.595
Disease duration, years	5 (2,8)	5 (3,8)	0.7
Diabetes mellitus, n (%)	53 (14.6%)	33 (22.6%)	0.03§
Hypertension, n (%)	119 (33%)	77 (52.7%)	< 0.001
Dyslipidemia, n (%)	17 (4.7%)	25 (17.1%)	< 0.001
Triglycerides, mg/dl	79 (61, 102)	101 (76, 135)	< 0.001
Cholesterol, mg/dl	171.49 (42.33)	168.38 (47.93)	0.545
Left Ventricular Ejection Fraction, %	48.7 (6.9)	48.5 (7.1)	0.773
Long-term home oxygen therapy, n (%)	50 (13.8%)	31 (21.2%)	0.04
pH	7.35 (0.09)	7.31 (0.11)	0.001
Required non- invasive ventilation, n (%)	30 (8.3%)	40 (27.4%)	< 0.001

AECOPD: acute exacerbations of COPD; IHD: ischemic heart disease.

† Subset of patients with AECOPD without comorbid IHD.

‡ Subset of patients with AECOPD with comorbid IHD.

§ Significant at P < 0.05



**Figure 1.** Comorbidity rates in patients with AECOPD with and without comorbid IHD.

AECOP: acute exacerbations of COPD; DM: diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease.

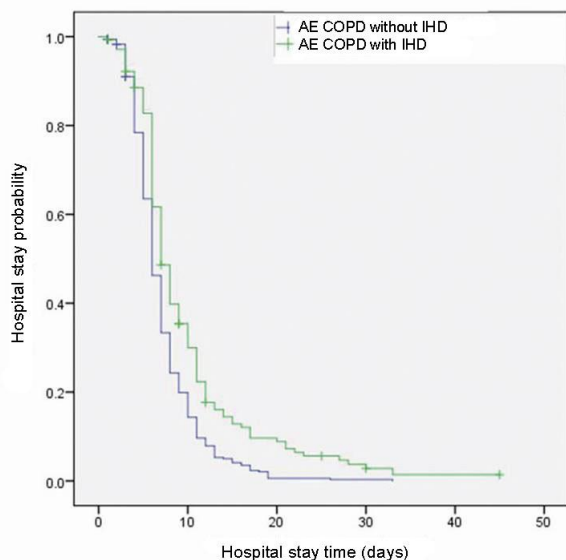
The median LOS was 7 days (IQR 6, 11) in patients with IHD versus 6 days (IQR 5, 8) for patients without IHD. The Kaplan-Meier method and log rank test for the comparison of LOS between patients with and without IHD revealed that there was a significant difference for LOS between patients with and without IHD (P<0.001). After adjusting for confounding factors, the LOS was 26% higher (95% CI: 1.03-1.44, P = 0.033) in patients with IHD (Table 2 and Figure 2).

**Table 2** Variables potentially associated with hospital stay: results of univariate and multivariate Cox regression analysis

Risk factors	Univariate	P- value	Multivariate	P- value
	hazard ratio 95%CI		hazard ratio 95%CI	
Age	1.72 (1.39-2.04)	<0.001†	1.51(1.29-1.86)	0.011
Gender	1.07 (0.87-1.40)	0.56	-	-
Smoking (packs/year)	0.99(0.97-1.01)	0.46	-	-
Diabetes	1.31(1.05-1.62)	0.01	1.27(1.04-1.46)	0.02
Hypertension	1.03(0.84-1.25)	0.79	-	-
IHD	1.28(1.02-1.46)	0.02	1.26(1.03-1.44)	0.033
Home oxygen therapy	1.56(1.33-2.08)	0.012	1.34(1.04-1.59)	0.025
pH	1.84(1.62-2.28)	< 0.001	1.72(1.48-2.02)	< 0.001

IHD: Ischemic heart disease.

† Significant at P< 0.05



**Figure 2.** Hospital stay curves for patients with AECOPD with and without comorbid IHD

AECOPD: Acute exacerbations of COPD; IHD: Ischemic heart disease.

The adjusted odds ratio (OR) for the risk of ICU admission for patients with IHD was 2.97 (95% CI: 1.81-4.89,  $P < 0.001$ ) compared to patients without IHD. Moreover, the adjusted OR for the risk of ICU admission for patients with pH  $< 7.35$  at the time of admission was 2.67 (95% CI: 1.61-4.44) and for long-term home oxygen therapy was 2.34 (95% CI 1.33-4.1) as shown in Table 3.

**Table 3.** Variables potentially associated with ICU admission: results of logistic regression analysis

Risk factors	Unadjusted OR 95%CI	P- value	Adjusted OR 95%CI	P- value
Age	1.3 (1.01-1.05)	0.001†	1.02(0.99-1.05)	0.14
Gender	1.42 (0.87-2.3)	0.15	1.006(0.46-2.1)	0.98
Smoking (packs/ year)	0.99(0.98-1)	0.045	1.001(0.98-1.01)	0.88
Diabetes	1.23(0.73-2.1)	0.428	-	-
Hypertension	1.78(1.2-2.7)	0.006	1.56(82-2.97)	0.44
IHD	2.7(1.8-4.2)	$< 0.001$	2.97(1.81-4.89)	$< 0.001$
Home oxygen therapy	3.9(2.4-6.6)	$< 0.001$	2.34(1.33-4.1)	$< 0.001$
pH	3.1(1.9-4.9)	$< 0.001$	2.67(1.61-4.44)	$< 0.001$

IHD: Ischemic heart disease.

† Significant at  $p < 0.05$

There were a few deaths in the study (10/146; 6.8%) among patients with IHD (7/361; 1.9% among patients without IHD); however, the risk of death in patients with IHD was greater than the risk of death in patients without IHD. The crude OR for the risk of death was 3.72 (95% CI: 1.4-9.98,  $P = 0.009$ ) and the adjusted OR was 3.86 (95% CI: 1.37-10.09) in patients with IHD.

## DISCUSSION

The results of this study showed that patients hospitalized with AECOPD and comorbid IHD had a higher LOS and greater risk of ICU admission and death than those with AECOPD without IHD. After adjustment for potentially confounding factors and other comorbidities, multivariate logistic regression and Cox regression analyses confirmed these results.

One plausible explanation for these poorer short-term outcomes is either IHD or higher prevalence of other comorbidities in COPD patients with IHD (4,14,15), may cause a more complicated course requiring longer hospital stay and increasing the risk of ICU admission and death. The markers of disease severity defined in the study including admission arterial blood gas pH  $< 7.35$ , long-term home oxygen therapy and requiring non-invasive mechanical ventilation were significantly higher in patients with AECOPD and comorbid IHD. Although there were no significant differences in age and smoking status between groups, the increased severity of COPD in these patients may be another possible explanation for prolonged LOS and increased risk of ICU admission and death.

Chronic obstructive pulmonary disease enhances the risk of developing HTN and DM. On the other hand, major risk factors of IHD including HTN, DM, hyperlipidemia and obesity, which are known as metabolic syndrome, have higher prevalence in COPD patients (4). In addition, chronic systemic inflammation promoting vascular endothelial dysfunction, atherosclerosis, physiological stress from comorbidities and acute inflammation following exacerbation may be responsible for the considerable rise of IHD prevalence in patients with COPD

(16-18). Based on these data, COPD patients with increased comorbidities, cardiovascular disorders and systemic inflammation can be considered as a subtype identified in recently published studies as "systemic COPD" (19) or "subtype C" (20); although the degree of severity of COPD in these patients remains controversial (11,14,21,22). While Garcia-Aymerich et al. reported moderate to severe airway obstruction with FEV1 of 58% predicted in stable state for "systemic COPD" (19), Arostegui et al. reported baseline mean FEV1 of 40.9% in exacerbation state for "subtype C" (20). Moreover, another issue with conflicting results is the relationship between the degree of severity of COPD and cardiovascular disease. While a number of studies indicate that the risk of cardiovascular disease is enhanced by an increase in the severity of COPD, in other studies, the results are less enlightening when adjusted for factors such as age and classic risk factors (14). Thus, further studies are required to investigate the features of this COPD subtype. Our results also indicate that patients with AECOPD and comorbid IHD can be considered a particular COPD subtype, because they have a more severe degree of COPD with poorer acute outcomes. This consideration may be important in optimal management of this particular COPD phenotype.

Factors that have been previously reported to be associated with a worse clinical outcome for patients hospitalized for AECOPD include aging (23), low arterial pH (24), male gender, requiring home oxygen, need for non-invasive ventilation and presence of comorbid conditions. Moreover, the main predictors of increased LOS are poor performance status, age of  $\geq 65$  years, interventions requiring assisted ventilation, lowest FEV1, oxygen saturation at admission of  $<86\%$ , an elevated blood glucose level and admission PEF of  $<150$  L/min (25). While the current study adjusted for most of these confounders, our results indicated that IHD could be considered as a prognostic factor for acute outcomes of patients hospitalized for AECOPD.

Comorbidity rates in the current study and those reported elsewhere were the same, with the exception of

dyslipidemia, which was lower in our study in comparison with previous studies (4,5,14,15). One explanation for this finding could be differences in race, lifestyle and obesity in the studied population.

The strength of this study was the inclusion of markers for disease severity that were not measured by Silver et al, (5) to evaluate the prevalence of comorbidities in patients hospitalized for COPD exacerbations and their impact on inpatient mortality. Even though the risk of death and ICU admission in the study by Silver et al. (5) was not significantly greater for patients with COPD exacerbations and IHD than for patients without comorbidities, the markers of disease severity can justify the different results of the two studies. However, additional investigations are required in this regard.

The importance of IHD as a major comorbidity of COPD was highlighted by the results of this study, which supports the view that IHD may be an adverse prognostic factor for patients hospitalized for AECOPD. Further studies are required to clarify the reasons for the poorer short-term outcomes in these patients and to determine optimal treatment for AECOPD and comorbid IHD and to find out whether proper management of IHD affects the clinical course of these patients.

## Disclosure

The authors have no conflicts of interest to declare.

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