Prevalence and Prognosis of Chronic Obstructive Pulmonary Disease Among 8167 Middle Eastern Patients With Acute Coronary Syndrome

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ABSTRACT

Background: The purpose of this study was to report the prevalence and the significance of clinically recognized chronic obstructive pulmonary disease (COPD) during acute coronary syndrome (ACS).

Hypothesis: COPD in patients with ACS is associated with worse outcome.

Methods: Data were derived from a prospective, multicenter, multinational study of 8167 consecutive patients hospitalized with ACS from February to June 2007 in 6 Middle Eastern countries. Data were analyzed according to the presence or absence of COPD. Demographic, management, and in-hospital outcomes were compared.

Results: The prevalence of COPD was 5.3%. When compared with non-COPD patients, COPD patients were older and more likely to have diabetes, hypertension, and dyslipidemia. Atypical presentations were more common in COPD patients ($P = 0.001$). COPD patients were less likely to be treated with thrombolytic therapy ($P = 0.001$), β-blockers ($P = 0.001$), and glycoprotein IIb/IIIa inhibitors, and more likely to receive angiotensin-converting enzyme (ACE) inhibitors. Although there was no difference in in-hospital mortality between the 2 groups, patients with COPD were more likely to have heart failure ($P = 0.001$). Despite the fact that COPD patients with ST-segment elevation myocardial infarction were less likely to receive thrombolytic therapy, they suffered more bleeding complications (2.8% vs 1%, $P = 0.04$), resulting in prolonged hospitalization. COPD was not an independent predictor of increased in-hospital mortality.

Conclusions: In this large cohort of patients with ACS, the prevalence of COPD was 5·3%. Atypical presentation is common among COPD patients, and this may result in delayed therapy. ACS in COPD patients was associated with higher risk of heart failure and major bleeding complications without increased risk of in-hospital mortality.

Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) among patients with acute coronary syndromes (ACS) and its influence on their outcomes is not well characterized. Previous studies suggested that COPD predisposes to the development of ischemic heart disease as a result of prolonged hypoxemia, while others maintained that patients with COPD had lower incidence of acute myocardial infarction (MI) due to the positive influence of hypoxemia on the development of the collateral circulation.[1–6]

In a recent large cohort of nearly 400 000 veterans with COPD admitted to a Veterans Administration (VA) hospital, the prevalence of coronary artery disease (CAD) was 33.6%, significantly higher than the prevalence seen in a matched cohort without COPD (27.1%).[7] Other investigators confirmed the high prevalence of CAD in patients with COPD.[8–12] More recently, epidemiologic evidence supports the importance of systemic inflammation in the pathogenesis of atheroma formation and ischemic heart disease, and recent studies have also indicated that patients with COPD have a prominent systemic inflammatory response.[10–16] C-reactive protein (CRP), a

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known marker of systemic inflammation, has been shown to be elevated in patients with both stable COPD and during exacerbation.[17–21] Because elevations in CRP have also been linked to CAD,[22] it appears as though the pathogenesis of both COPD and CAD may stem from enhanced systemic inflammation. Interestingly, although the mortality rate from cardiovascular diseases is decreasing in the developed world, the mortality rate from COPD is in fact increasing, and COPD is the fourth leading cause of death in the United States. Furthermore, the leading causes of hospitalization and mortality among COPD patients are cardiovascular events.

The aim of the current study is to identify the characteristics, clinical management, and in-hospital outcome of ACS patients with and without COPD and to test the hypothesis that patients with COPD developing ACS are at increased risk of subsequent in-hospital cardiac events.

Methods

The Gulf Registry of Acute Coronary Events (Gulf RACE) is the largest multinational registry of acute coronary events in the Middle East. Over a 6-month period, it prospectively enrolled 8169 consecutive patients with ACS from 65 centers in 6 adjacent Middle Eastern Gulf countries (Bahrain, Kuwait, Qatar, Oman, United Arab Emirates, and Yemen). All patients had a final diagnosis of ACS, including unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). The majority of hospitals (73%) had coronary care units on-site. An on-site cardiac catheterization laboratory was available in 30% of hospitals, and 31% of hospitals had a laboratory available within a 60-minute drive. The study received ethical approval from the institutional ethics bodies in all participating countries, and all patients gave informed consent to process their de-identified data. There were no exclusion criteria, and all the prospective patients were actually enrolled. Full details of the methods have been published.[22–24] Diagnosis of the different types of ACS and definitions of data variables were based on the American College of Cardiology (ACC) clinical data standards.[25–26] Recruitment in the pilot phase started on May 8, 2006, and continued for 30 days. Enrollment in the next phase of the registry started on January 29, 2007, and continued for 5 months.

COPD Classification

Because this study was an observational investigation of outcomes after patients' presentation with ACS, pulmonary function tests were not routinely performed to diagnose and quantify the severity of COPD. Instead, any patient with a documented history of obstructive pulmonary disease (i.e., COPD or asthma) or treatment with pharmacologic therapies specific for obstructive lung disease (inhaled steroids, inhaled anticholinergics, inhaled β-agonists, or theophylline) were considered to have COPD.[27]

Statistical Analysis

Baseline and clinical characteristics of patients were presented as median and 25th and 75th percentiles for continuous variables, whereas frequency distribution and percentages have been presented for categorical variables. Independent t tests were used for comparing continuous variables, and χ^2 tests for categorical variables have been used for comparing COPD vs non-COPD cases. A univariate logistic regression was performed for all important variables, and a P value ≤ 0.15 was considered to include in multivariate logistic regression analysis to see importance of COPD in hospital mortality. To see significant variation in the prevalence of current smokers among ACS patients in the 6 countries, a χ^2 test was performed. A P value of <0.05 was considered statistically significant in the study. All data analyses were carried out using SPSS version 14 (SPSS Inc, Chicago, IL).

Results

Study Population Characteristics

We enrolled 8169 patients who were admitted with ACS, and complete data was successfully obtained in 8167 patients; 3199 patients (39.2%) were diagnosed with STEMI, 2693 patients (32.1%) with NSTEMI, and 2628 (28.7%) with unstable angina. Overall, 434 patients (5.3%) had a diagnosis of COPD.

Presenting Symptoms and Baseline Clinical Characteristics

When compared with non-COPD patients, patients with COPD were older (median and 25th and 75th percentiles 64 [56–71] vs 55 [47–64], $P = 0.001$) (Table 1). Patients with COPD were more likely to have past cardiovascular history including angina, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting, and more likely to be on aspirin. They were also more likely to have hypertension, diabetes, hyperlipidemia, and higher body mass index, and have more advanced functional Killip class >I heart failure on presentation. COPD patients were more likely to present with atypical chest pain, palpitation, and dyspnea than with typical chest pain. COPD patients had significant delay in their presentation (>12 hours) and had a higher basal heart rate when compared with non-COPD patients.

In-hospital Treatment and Outcome

Thrombolytic treatment was the primary reperfusion therapy used in patients with STEMI. After hospital admission, there were differences in the medical and invasive management provided to patients based on the presence and absence of COPD (Table 2 and Table 3). Patients with

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Table 1. Baseline Clinical Characteristics in Acute Coronary Syndrome Patients With and Without COPD

Characteristics	COPD	Non-COPD	*P* Value
No. of patients (%)	434 (5.3)	7733 (94.7)	NA
No. of deaths	13	279	NA
Mortality rate	3.0%	3.6%	0.50
Age (y)	64 (56–71)	55 (47–64)	0.001
Past CVD history			
Angina	236 (54.4)	3073 (39.7)	0.001
MI	151 (34.8)	1841 (23.8)	0.001
PCI	67 (15.4)	890 (11.5)	0.013
CABG	41 (9.4)	420 (5.4)	0.001
Aspirin use	234 (53.9)	3092 (40.0)	0.001
Cardiovascular risk factors			
Diabetes mellitus	209 (48.2)	3094 (40.0)	0.001
Hypertension	278 (64.2)	3761 (48.6)	0.001
Dyslipidemia	167 (38.6)	2433 (31.4)	0.002
Current smoker	168 (38.7)	2813 (36.3)	0.32
Killip class >I	167 (38.6)	1609 (20.8)	0.001
Presenting symptoms			
Symptoms onset ≤12 h	74 (54.8)	2157 (70.8)	0.001
Ischemic-type chest pain	277 (63.8)	6206 (80.3)	0.001
Atypical chest pain	35 (8.1)	501 (6.5)	0.001
Dyspnea	93 (21.4)	707 (9.1)	0.001
Palpitation	11 (2.5)	73 (0.9)	0.001
Loss of consciousness	7 (1.6)	165 (2.1)	0.001
Others	168 (2.1)	11 (2.5)	0.001
Vital signs at admission			
Heart rate (bpm)[a]	90 (77–110)	82 (70–97)	0.001
Systolic blood pressure (mm Hg)[a]	140 (120–160)	139 (120–160)	0.06
Body mass index (mean)	29.1 ± 7	27.5 ± 5	0.001
First blood sugar (mmol/L)[a]	8.4 (6.2–13.1)	7.8 (5.9–12.2)	0.29
Fasting blood sugar (mmol/L)[a]	6.4 (5.3–8.5)	6.3 (5.3–9.1)	0.70

Abbreviations: CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; NA, not applicable; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
[a] Median.

Table 2. In-hospital Therapy and Discharge Therapy in Acute Coronary Syndrome Patients With and Without COPD

Characteristics	COPD, N (%)	No COPD, N (%)	*P* Value
Primary PCI	3 (2.9)	47 (3.0)	0.88
Median door-to-needle time (min)	60 (0–40)	76.9 (0–50)	0.43
Medications			
Thrombolysis	49 (36.8)	1810 (59.1)	0.001
Aspirin	417 (96.1)	7578 (97.9)	0.01
β-Blocker	127 (29.3)	5188 (67.1)	0.001
ACEI/ARB	306 (70.5)	4889 (63.2)	0.002
Clopidogrel	206 (47.5)	5153 (53.7)	0.012
Unfractionated heparin	156 (43)	3004 (47.5)	0.07
Low–molecular-weight heparin	189 (52)	2981 (47)	0.08
GP2b3a	24 (5.5)	854 (11.0)	0.001
Statin	308 (84)	5111 (81)	0.12

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; GP2b3a, glycoprotein IIb/IIIa inhibitor; min, minutes; PCI, percutaneous coronary intervention; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Table 3. In-hospital Outcome in Acute Coronary Syndrome Patients With and Without COPD

Variables	COPD, n (%)	Non-COPD, n (%)	*P* Value
Death	13 (3.0)	279 (3.6)	0.50
Congestive heart failure	112 (25.8)	1212 (15.7)	0.001
Cardiogenic shock	22 (5.1)	393 (5.1)	0.99
Myocardial reinfarction	7 (1.6)	192 (2.5)	0.25
Stroke	3 (0.7)	53 (0.7)	0.98
Median hospital stay (d)	7 (4–8)	6 (3–7)	0.001

Abbreviations: COPD, chronic obstructive pulmonary disease.

COPD were less likely to receive thrombolytic therapy, glycoprotien IIb/IIIa inhibitors, and β-blocker therapy. COPD patients were more frequently prescribed angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs). There were no significant differences between the 2 groups in regard to use of unfractionated heparin, low-molecular-weight heparin, or statin therapy. Patients with COPD frequently had congestive heart failure (CHF) during hospitalization (25.8% vs 15.7%, $P = 0.001$), with no statistical difference in cardiogenic shock, in-hospital mortality rate, stroke, or reinfarction. COPD patients had longer hospital stays than non-COPD patients (7 days [4–8] vs 6 days [3–7], $P = 0.001$), and in the STEMI group the incidence of major bleeding complications was higher in the COPD group (2.8% vs 1%, $P = 0.04$), despite the fact that these patients were less likely to receive thrombolytic therapy.

Multivariate Predictors of Outcome

Multivariate predictors of in-hospital mortality for all ACS patients demonstrated age, female gender, and cardiogenic shock to be independent predictors of increased in-hospital mortality, whereas thrombolytic therapy, β-blockers, ACE inhibitors or ARBs, and aspirin use were shown to be associated with reduced mortality. COPD was not an independent predictor of in-hospital outcome (Table 4). There was a significant association between in-hospital mortality and major bleeding complications (odds

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Table 4. Multivariate Analysis for Factors That Predict In-hospital Mortality in Patients With Acute Coronary Syndrome

Variable	OR	95% CI	*P* Value
Female gender	1.76	1.1–2.8	<0.01
Age (per year)	1.05	1.03–1.07	<0.01
Cardiogenic shock	58.9	39.0–88.6	<0.01
COPD	0.40	0.20–1.24	0.13
Thrombolysis	0.45	0.30–0.67	<0.01
Aspirin	0.25	0.12–0.70	0.008
β-Blocker	0.37	0.23–0.59	<0.001
ACEI	0.43	0.28–0.65	<0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

ratio [OR]: 3.3, 95% confidence interval [CI]: 1.66–6.76, $P = 0.001$).

Discussion

The current study confirms previous reports of a 5%–6% prevalence of COPD among patients presenting with ACS in a real-world registry (Table 5). Furthermore, it reports for the first time that COPD patients with ACS frequently present with atypical presentations (mainly dyspnea) that could be misinterpreted as COPD exacerbations. In addition, although COPD was associated with an older age group and worse cardiovascular risk profile, COPD was not independently associated with increased in-hospital mortality; however, it was associated with higher incidence of CHF, which is concordant with a study by Kjøller et al[28] reporting a 28% prevalence of CHF among patients with COPD admitted with MI. Finally, although COPD patients presenting with STEMI were less likely to receive reperfusion therapy, they had a higher risk of major bleeding complications.

Although both coronary atherosclerosis and chronic obstructive pulmonary diseases are highly prevalent worldwide and share a very important risk factor—smoking—studies on the prevalence of COPD among patients with coronary disease and its influence on the course of acute MI are scarce. In 1964, in a postmortem study of 290 patients with acute MI, only 4 instances of possible coexistence with obstructive emphysema were detected (<2%). In the same study, Nonkin et al[1] reported that the distribution of coronary artery atherosclerosis among 104 patients with chronic obstructive pulmonary emphysema appeared to be similar to that of other groups of similar ages. In a clinical investigation among 389 patients with COPD age 40 years and older, there was no statistically significant difference in the prevalence of MI in patients with chronic lung disease compared with a control group.[3] Interestingly, a more recent study by Izbicki et al[29] reported differences in the prevalence of coronary atherosclerosis between various chronic lung diseases in patients undergoing cardiac evaluation for lung transplantation. Patients with lung fibrosis had a higher prevalence of coronary atherosclerosis than did patients with emphysema (28.6% vs 9.8%, $P = 0.019$), despite the fact that smoking was much more prevalent in patients with emphysema. The investigators hypothesized that the inflammatory process in lung fibrosis may involve the coronary arteries as part of a systemic inflammation rather than an idiopathic fibrotic process confined to the lung.

The associations between stable and unstable coronary artery disease and COPD have been reported in limited number of studies (Table 5).[27,28,30–34] Behar et al,[33] using data from the Secondary Prevention Reinfarction Israel Nifedipine Trial (SPRINT) study, which was conducted between 1981 and 1983, reported a 7% prevalence of COPD among 5839 survivors of MI. The age group of the SPRINT study was comparable to that of the current study, and the investigators reported increased incidence of prior history of angina and smoking. In the SPRINT study, although COPD patients had a higher incidence of in-hospital and long-term mortality, COPD was not an independent predictor of increased mortality. Moreover, COPD patients had a higher risk of developing CHF as well as paroxysmal atrial fibrillation and advanced atrioventricular block. The current study extends these findings in a larger cohort of patients from another part of the Middle East in the current era, where significant improvements have occurred in the understanding and therapy of both COPD and ACS over that available in the 1980s. Furthermore, it reports for the first time a high prevalence of atypical presentations (mainly dyspnea) in up to 32% of these patients, which could be misdiagnosed as COPD exacerbation; this in part may explain underdiagnosis of MI in COPD patients reported previously by Brekke et al.[35] Previous studies included an older age group than the Gulf RACE with variable incidence of smoking history, other cardiovascular risk factors, and ethnicities that could explain the variability between the findings of SPRINT and the current study. We observed increased major bleeding complications in COPD patients with STEMI. This was not reported before, and occurred despite the fact that COPD patients were less likely to receive thrombolytic therapy. This increased risk may be explained by the fact that these patients were more likely to receive additional therapy (ie, bronchodilators and corticosteroids) that may interact with antiplatelet and antithrombotic medications and increase bleeding risk. This is supported by observations from a population-based cohort study from Denmark which reported increased risk of hospitalization because of

Table 5. Prevalence and Impact of COPD on Patients With ACS or Stable Coronary Artery Disease in Reported Studies

Author	Study	No. of Patients	COPD Prevalence (%)	Smoking (%)[a]	Age Mean ± SD (y)[a]	Mortality Rate/Comments
Stable coronary artery disease						
Nishiyama et al, 2009[30]	CREDO-Kyoto Registry (Japan)	PCI (n = 6878) or CABG (n = 2999)	2.4	43.8 vs 35.7		No difference in in-hospital mortality for COPD vs non-COPD (1.3% vs 1.2%, $P = 0.9$). At 3-y follow-up, COPD associated with higher incidence of all-cause mortality ($P < 0.0001$), cardiovascular death ($P = 0.0002$), and cardiac death ($P < 0.0001$).
Selvaraj et al, 2005[31]	PCI (1997–2003)	10 994	10	27.0 vs 18.0	67.63 ± 0.58 vs 64.11 ± 0.23	COPD an independent predictor of in-hospital death (OR 2.51, 95% CI: 1.45–4.35, $P < 0.001$) and long-term mortality (HR 2.16, 95% CI: 1.81–2.56, $P < 0.0001$) after PCI.
Berger et al, 2004[32]	PCI (1998–1999), New York City	4248	4.3	30 vs 22	66.1 ± 10.7 vs 63.3 ± 12.0	In-hospital outcome not different, but at 3-y follow-up, mortality rate with COPD was 21% vs 9% for non-COPD, $P < 0.001$.
Acute coronary syndrome (ACS)						
Behar et al, 1992[33]	SPRINT Registry (Israel)	5839	7	44.3 vs 30.7	66.8 ± 9.7 vs 62.7 ± 10.8	Mortality rates (COPD vs non-COPD): in-hospital, 23.9% vs 17.2%; at 1 y, 12.3% vs 9.2%; at 5 y, 35.9% vs 26.9%. $P < 0.005$ for in-hospital and 5 y.
Dziewierz et al, 2009[34]	Malopolska Registry of ACS (Poland)	STEMI 334, NSTEMI 380	STEMI 9.3, NSTEMI 13.2	STEMI 36.5, NSTEMI 30	70.2 ± 11.6 vs 66.3 ± 13.6	Multivariate Cox regression analysis for in-hospital death for COPD (OR: 2.25, 95% CI: 1.36–3.71, $P = 0.002$).
Salisbury et al, 2007[27]	PREMIER study (USA)	2498 with MI discharged alive	15.6	37.6 vs 33.3	64.5 ± 12.4 vs 60.1 ± 13.0	1-y mortality (COPD vs non-COPD) 15.8% vs 5.7%, $P < 0.001$. (After adjustment HR: 2, 95% CI: 1.44–2.79).
Kjøller et al, 2004[28]	TRACE study (Denmark)	6669	11.5	COPD 60.0, non-COPD 50.4	70.5 vs 68.2	30-d and 5-y survival, COPD 86.3% and 42.9% vs non-COPD 87.7% and 57.5%, RR = 1.49 (1.35–1.65). The prevalence of congestive heart failure was 65.9% in COPD patients vs 52.0% in non-COPD patients.
Current study	Gulf RACE (Middle East)	8190	5.3	Overall ACS 38, STEMI 52, NSTEMI 29	61.1 ± 11.6 vs 53.9 ± 12.1	In-hospital mortality rate (COPD vs non-COPD) 3% vs 3.6%, P = NS.

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CREDO, Clopidogrel for Reduction of Events During Observation trial; Gulf RACE: Gulf Registry of Acute Coronary Events; HR, hazard ratio; PCI, percutaneous coronary intervention; NS, not significant; NSTEMI, non–ST-segment elevation myocardial infarction; OR, odds ratio; PREMIER, Prospective Registry Evaluating Myocardial Infarction: Event and Recovery study; RR, relative risk; SPRINT, Secondary Prevention Reinfarction Israeli Nifedipine Trial; STEMI, ST-segment elevation myocardial infarction; TRACE, Trandolapril Cardiac Evaluation Study.

[a] COPD group vs non-COPD group.

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upper-gastrointestinal bleeding among patients prescribed corticosteroids, especially among those who use antiplatelet therapy.[36] Unfortunately, documentation of medications used to treat COPD was not reported in the current study, and further studies are required to evaluate the validity of this interaction.

The current study demonstrates low use of β-blocker therapy in ACS patients with COPD, which is consistent with previous studies,[32,37–39] despite the fact that the use of highly selective β-blockers has been shown to be useful and effective in the majority of COPD. Chen et al[40] examined the relationship between after-discharge use of β-blockers and 1-year mortality in patients with COPD, using data from the Cooperative Cardiovascular Project. Of the 54 962 patients with no contraindications to β-blockers, patients with COPD or asthma (20%) were significantly less likely to be prescribed β-blockers at discharge after acute MI. After adjusting for demographic and clinical factors, the investigators found that β-blocker use was associated with lower 1-year mortality in patients with COPD or asthma.

The impact of COPD on patients with stable coronary artery disease has been reported in several studies which reported COPD to be an independent predictor of poor long-term outcome. Finally, several recent studies suggested that bronchodilator therapy and oral corticosteroid use in COPD patients may increase their risk of developing myocardial infarction,[41] highlighting the need for further studies in this important group of patients.

Study Limitations

Our data were collected from an observational study. The fundamental limitations of observational studies cannot be eliminated because of the nonrandomized nature and unmeasured confounding factors. However, well-designed observational studies provide valid results and do not systematically overestimate the results compared with the results of randomized controlled trials. Interestingly, in the current study there were no significant differences in the prevalence of current smokers between the COPD and non-COPD groups; but it is possible that there were more previous smokers or secondhand smokers among patients with COPD, two important variables that were not recorded in the current registry. However, these two variables would not affect the impact of COPD on patients presenting with ACS. Long-term follow-up is needed in both groups to fortify our findings. Finally, documentation of medication use to treat COPD was lacking in this registry, highlighting the importance of studying the interaction between ACS and COPD medications in future prospective studies.

Clinical Implications

In this large cohort of patients with ACS, the prevalence of COPD was 5.3%. Atypical presentation is common among COPD patients, and this may result in delayed therapy. ACS in COPD patients was associated with higher risk of heart failure and major bleeding complications without increased risk of in-hospital mortality.

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