

# Relationship between chronic obstructive pulmonary disease and in-hospital management and outcomes in patients with acute myocardial infarction

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## Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) is associated with unfavourable short- and long-term outcome in patients with coronary artery disease undergoing revascularisation procedures.

**Aim:** To assess the associations of COPD with in-hospital management and mortality in patients with acute myocardial infarction (MI) admitted to hospitals without on-site invasive facilities.

**Methods:** We identified 81 (11.3%) patients with COPD and 633 (88.7%) without COPD treated in the Krakow Registry of Acute Coronary Syndromes from February 2005 to March 2005 and from December 2005 to January 2006. Data concerning in-hospital management and mortality were assessed.

**Results:** Patients with COPD were older and were more likely to have prior angina, prior heart failure symptoms, prior stroke, and lower left ventricular ejection fraction. Patients with COPD diagnosis were less likely to be transferred for invasive treatment [COPD (–) vs. COPD (+), 12.3 vs. 34.9%;  $p < 0.0001$ ] and to receive aspirin and clopidogrel during index hospital stay. In-hospital mortality was higher in patients with COPD diagnosis [COPD (–) vs. COPD (+), 58 of 412 (14.1%) vs. 21 of 71 (29.6%);  $p = 0.002$ ]. COPD was an independent predictor of in-hospital death in multivariate Cox regression analysis.

**Conclusions:** Coexistence of COPD with acute MI may be associated with less frequent transfer for invasive treatment, less aggressive pharmacotherapy, and higher in-hospital mortality in patients admitted to community hospitals without on-site invasive facilities. These differences may be partially driven by a higher risk profile of COPD patients.

**Key words:** chronic obstructive pulmonary disease, acute myocardial infarction, management, mortality

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a very common, smoking-related disease characterised by persistent airway obstruction due to chronic bronchitis or emphysema [1]. Importantly, COPD is now the fourth leading cause of death in the United States and Europe, and it is the only common cause of death that is increasing in incidence [1]. In industrialised countries cigarette smoking accounts for most cases of COPD, and as cigarette smoking is a well-known risk factor for coronary artery disease (CAD), it is expected that a considerable number of patients hospitalised with CAD diagnosis also have concomitant COPD [1]. In previous studies coexistence of COPD was associated with unfavourable outcome in patients after myocardial infarction (MI) [2], and in patients

with CAD undergoing percutaneous coronary intervention (PCI) [3, 4] or coronary artery bypass grafting (CABG) [5, 6].

To the best of our knowledge, this is one of the first studies examining the associations between COPD and in-hospital management and mortality in patients with acute MI admitted to hospitals without on-site invasive facilities.

## Methods

The Krakow Registry of Acute Coronary Syndromes was a prospective, multicentre, observational registry designed to examine current epidemiology, in-hospital management and outcome of patients with acute coronary syndromes in this region of Poland (Krakow, Malopolska Region). The design of the Registry was described previously [7, 8]. Cardiogenic shock was defined as reduced blood pressure

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(systolic blood pressure < 90 mmHg or a drop of mean arterial pressure by > 30 mmHg) and/or low urine output (< 0.5 ml/kg/h), with a pulse rate > 60 beats per minute with or without evidence of organ congestion [9]. Patients were classified as NSTEMI and STEMI based on their final diagnosis. STEMI was diagnosed if ST-segment elevation  $\geq 1$  mm occurred in  $\geq 1$  lead or new left bundle branch block was found in the electrocardiogram with biochemical evidence of myocardial necrosis ( $\geq 1$  positive biochemical cardiac necrosis marker measurement). NSTEMI was diagnosed in patients with  $\geq 1$  positive biochemical cardiac necrosis marker measurement without new ST-segment elevation in the electrocardiogram. Patients with previous history of COPD treated with bronchodilators or steroids at index hospital admission were classified as COPD patients. All-cause in-hospital mortality was assessed in patients remaining in community hospitals for conservative treatment. Occurrence of other ischaemic and bleeding events was also analysed in this group of patients.

### Statistical analysis

Data were analysed according to the established standards of descriptive statistics. Continuous variables are expressed as mean  $\pm$  standard deviation. Categorical variables are presented as percentages. Statistical comparisons between groups were performed using  $\chi^2$  test and Fisher's exact test for categorical variables and independent samples Student's t-test for continuous variables, as appropriate. Additionally, frequency of transfer for invasive treatment and in-hospital mortality was

assessed in pre-specified groups (age  $\leq 75$  vs. > 75 years, cardiogenic shock vs. no cardiogenic shock presence, NSTEMI vs. STEMI final diagnosis) and the Breslow-Day test for homogeneity was used to prove possible interactions. Multivariate Cox regression analysis was performed to find significant predictors of in-hospital death. Forward selection in Cox regression with the probability value for covariates to enter the model was set at the level of 0.05. The following covariates were tested: age, gender, body mass index, presence of diabetes mellitus, arterial hypertension, hyperlipidaemia, prior angina, prior MI, prior heart failure symptoms, left ventricular ejection fraction (LVEF), prior PCI, prior CABG, prior stroke transient ischaemic attack, history of smoking, peripheral arterial disease, chronic renal insufficiency, COPD, parameters on admission (chest pain presence, cardiogenic shock presence, heart rate, systolic blood pressure, diastolic blood pressure), time from chest pain onset to admission and final diagnosis (STEMI, NSTEMI). Risk of in-hospital death was expressed as hazard ratio with 95% confidence intervals. All tests were 2-tailed, and a p value of < 0.05 was considered statistically significant.

### Results

The Krakow Registry of Acute Coronary Syndromes database included 1414 patients with acute coronary syndrome admitted between February 2005 and March 2005, and between December 2005 and January 2006. A total of 700 patients with final diagnosis other than MI (e.g. unstable angina, stable angina, extracardiac cause of

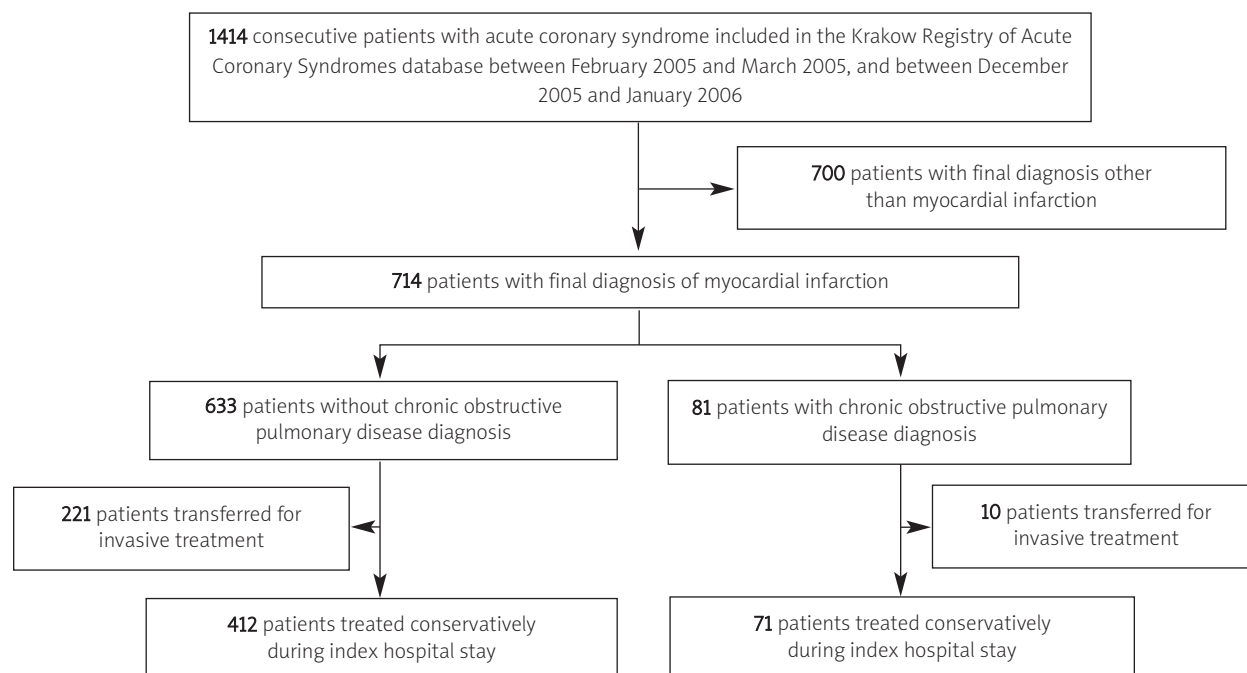


Figure 1. Scheme of groups' distribution in the registry

chest pain) were excluded from the analysis. COPD was diagnosed in 81 (11.3%) of the remaining 714 patients (Figure 1). Baseline demographic and clinical characteristics of patients with and without COPD diagnosis are summarised in Table I. Patients with COPD were older and were more likely to have prior angina, prior heart failure symptoms, prior stroke, and lower LVEF. Heart rate on admission was higher and diastolic blood pressure on admission was lower in patients with COPD. As shown in Table I there was no difference in discharge diagnosis and cardiogenic shock rates between study groups.

Patients with COPD diagnosis were less likely to be transferred for invasive treatment during index hospital stay than patients without COPD [221 of 633 (34.9%) vs. 10 of 81 (12.3%);  $p < 0.0001$ ]. The proportions of transferred patients with and without COPD stratified by age, cardiogenic shock presence on admission, and discharge diagnosis are shown in Figure 2 A.

As shown in Table II patients with COPD diagnosis were less likely to receive aspirin and clopidogrel during index hospital stay. Use of other pharmacological agents, including beta-blockers, was similar among study groups.

Among patients treated conservatively during index hospital stay, in-hospital mortality was higher in patients with COPD diagnosis [COPD (-) vs. COPD (+), 58 of 412 (14.1%) vs. 21 of 71 (29.6%);  $p=0.002$ ]. In-hospital mortality for patients with and without COPD stratified by age, cardiogenic shock presence on admission, and discharge diagnosis is shown in Figure 2B. Tests for interaction and multivariate Cox regression analysis (see Table III) have confirmed that COPD diagnosis was independently associated with in-hospital mortality in patients with acute MI treated conservatively during index hospital stay.

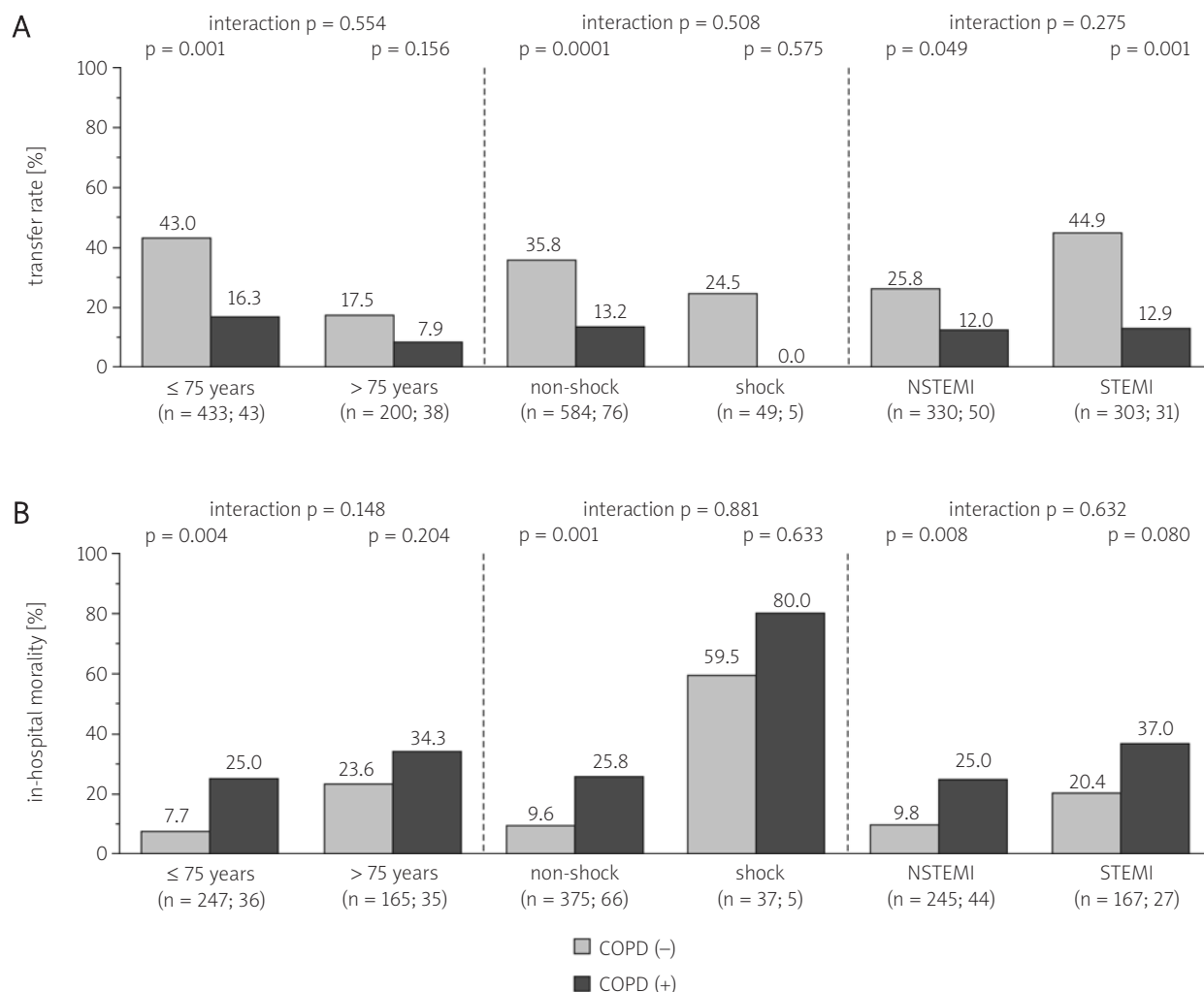
Among patients remaining in remote hospitals, patients with COPD diagnosis were at higher risk of atrial fibrillation [COPD (-) vs. COPD (+), 2.2 vs. 7.0%,  $p = 0.041$ ]

**Table I.** Baseline demographic and clinical characteristics

Parameters	COPD (-) n = 633	COPD (+) n = 81	p
Male	60.0%	61.7%	0.8
Age [years]	67.9 ± 12.9	71.8 ± 10.7	0.003
Age > 75 years [%]	31.6	46.9	0.008
Body mass index [kg/m <sup>2</sup> ]	27.3 ± 7.1	26.1 ± 4.0	0.1
Diabetes mellitus [%]	23.1	23.5	1
Arterial hypertension [%]	70.6	76.5	0.3
Hyperlipidaemia [%]	47.1	37.0	0.1
Prior angina [%]	55.5	80.2	< 0.0001
Prior myocardial infarction [%]	28.6	34.6	0.3
Prior heart failure symptoms [%]	19.3	30.9	0.019
Prior percutaneous coronary intervention [%]	5.8	4.9	0.8
Prior coronary artery bypass graft [%]	2.5	0.0	0.2
Prior stroke/transient ischaemic attack [%]	6.6	13.6	0.039
Current smoker [%]	32.1	40.7	0.1
Family history of coronary artery disease [%]	13.3	16.0	0.6
Peripheral arterial disease [%]	11.7	14.8	0.5
Chronic renal insufficiency [%]	6.2	11.1	0.1
Chest pain on admission [%]	67.5	61.7	0.3
Time from chest pain onset to admission [hours]	14.7 ± 19.5	14.7 ± 20.3	0.9
Time from chest pain onset to admission ≤ 12 hours [%]	68.4	70.1	0.8
Heart rate on admission [beat/min]	84.8 ± 24.3	93.8 ± 26.3	0.002
Systolic blood pressure on admission [mmHg]	142.0 ± 35.2	137.0 ± 35.0	0.2
Diastolic blood pressure on admission [mmHg]	87.1 ± 16.6	83.6 ± 16.2	0.1
Cardiogenic shock on admission [%]	7.7	6.2	0.7
Left ventricular ejection fraction [%]	49.8 ± 13.3	44.6 ± 13.7	0.005
Discharge diagnosis of STEMI [%]	47.9	38.3	0.1

Values are presented as percentages or mean ± SD.

Abbreviations: COPD – chronic obstructive pulmonary disease, STEMI – ST-segment elevation myocardial infarction



**Figure 2.** Proportion of patients transferred for invasive treatment (A) and in-hospital mortality (B) in patients without (gray bars) and with (black bars) chronic obstructive pulmonary disease (COPD) stratified by age, cardiogenic shock presence on admission, and discharge diagnosis

and ventricular tachycardia/ventricular fibrillation (1.5 vs. 7.0%,  $p = 0.014$ ) occurrence during index hospital stay. Rates of 2<sup>nd</sup> and 3<sup>rd</sup> grade atrioventricular block (1.7 vs. 0.0%,  $p = 0.601$ ), pulmonary oedema (5.6 vs. 9.9%,  $p = 0.288$ ), ischaemic stroke (1.0 vs. 2.8%,  $p = 0.216$ ), and blood transfusion (2.4 vs. 2.8%,  $p = 0.692$ ) were similar in the study groups.

**Discussion**

Our study is the first to date showing that patients with acute MI and concomitant COPD are less frequently treated with antiplatelet agents, as well as transferred for invasive treatment, and experience higher in-hospital mortality than patients without COPD. In our registry, more than 1 in 10 patients admitted with acute MI had already the diagnosis of COPD. In previous studies the frequency

of COPD ranged from 4.3% in patients with CAD undergoing PCI [3], 15.6% in patients after MI [2], up to 26.1% in patients with CAD undergoing CABG [5]. Similarly to previous reports, COPD patients were older and were more likely to have had higher prevalence of age-related and smoking-related comorbidities [1, 3-6]. For example, prior stroke was more frequently observed in patients with COPD than in patients without COPD [1, 3, 4]. Importantly, reduced lung function has been shown to be a significant predictor of non-fatal and fatal stroke [10, 11].

We have confirmed that COPD patients were less likely to be transferred for invasive diagnostics and treatment during index hospital stay. This difference in the proportion of transferred patients may be driven by the difference in baseline characteristics, especially higher age and more frequent prevalence of other comorbidities in COPD patients,

**Table II.** Pharmacological treatment during hospital stay

Characteristics	COPD (-) n = 633	COPD (+) n = 81	p
Aspirin [%]	96.7	86.4	< 0.0001
Clopidogrel [%]	19.1	8.6	0.020
Ticlopidine [%]	16.6	18.5	0.8
Glycoprotein IIb/IIIa inhibitor [%]	5.8	1.2	0.1
Thrombolysis [%]	8.4	3.7	0.2
Low-molecular-weight heparin [%]	72.2	81.5	0.1
Beta-blocker [%]	69.4	72.8	0.5
Angiotensin-converting enzyme inhibitor / angiotensin II antagonist [%]	66.2	63.0	0.6
Calcium antagonist [%]	7.0	6.2	0.8
Nitrates [%]	64.5	63.0	0.8
Statins [%]	77.4	79.0	0.8

Values are presented as percentages.

Abbreviations: COPD – chronic obstructive pulmonary disease

**Table III.** Multivariate Cox regression analysis for in-hospital death

Variable	Hazard ratio	95% confidence interval	p
Age (per 1 year)	1.03	1.01-1.06	0.005
Cardiogenic shock	5.04	3.06-8.29	< 0.001
Chronic obstructive pulmonary disease	2.15	1.30-3.55	0.003
STEMI (vs. NSTEMI)	1.87	1.20-2.92	0.006

Results are presented as hazard ratios with 95% confidence intervals.

Abbreviations: STEMI – ST-segment elevation myocardial infarction, NSTEMI – non-ST-segment elevation myocardial infarction

which may influence the decision concerning transfer for invasive treatment. On the other hand, patients with COPD may receive less aggressive invasive diagnostics and revascularisation procedures due to the fear of increased periprocedural mortality in those patients who have undergone CABG [5, 6] or PCI [3, 4]. We expect that in the remaining, conservatively treated cohort there were a lot of patients who would have benefited from the invasive strategy. In COPD patients, especially with exacerbation of COPD symptoms, acute MI can also be unrecognised and due to atypical presentation may be associated with no reperfusion treatment or longer time delays to reperfusion therapy [12].

Regardless of the risk profile (age, cardiogenic shock, discharge diagnosis) COPD was associated with a more than twofold increase in in-hospital mortality in patients with acute MI treated conservatively. There are many potential mechanisms responsible for poor short- and long-term prognosis in patients with CAD and COPD. First of all, it is still debatable whether COPD itself poses a risk for patients with CAD, or it is only a benign marker of disease severity. COPD is frequently associated with advanced age and higher prevalence of age-related diseases (e.g. renal insufficiency, diabetes mellitus, stroke), which have themselves been shown to be associated with adverse outcomes in patients

with CAD, especially patients with acute coronary syndromes [13-16]. Moreover, we have found that COPD patients were less likely to receive guideline-recommended therapies, including acute aspirin and clopidogrel. On the other hand, the observed difference in antiplatelet treatment may be partially related to the difference in baseline characteristics (i.e. age) and concomitant medication use. A lower rate of beta-blockers use was also reported in previous studies in patients with COPD [2, 4, 17]. There is reluctance to use them in patients with COPD, due to the expected adverse reactions and bronchospasm. As in the more recent studies the observed benefits of cardioselective beta-blockers in COPD patients appear to outweigh any potential risk of side effects, they should not be withheld in COPD patients [18]. Importantly, the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry data [19, 20], as well as our previous report [7], demonstrated that patients who present with acute coronary syndrome and do not receive guideline-recommended therapies (including aspirin, clopidogrel, and beta-blocker) have a higher mortality rate.

In addition, the use of inhaled beta-agonists among COPD patients could also contribute to the elevated arrhythmia risk, which potentially may influence in-hospital



outcome. In our cohort the risk of atrial fibrillation and ventricular tachycardia/ventricular fibrillation was higher among COPD patients, but due to the lack of information concerning current COPD treatment the interaction between such treatment and arrhythmia risk was not possible to assess. On the other hand, a link between COPD and systemic inflammatory response, confirmed by elevated plasma levels of acute phase proteins, i.e. C-reactive protein, interleukin-6, and fibrinogen, was suggested [21]. That way COPD may hasten the progression of atherosclerotic disease as well as the destabilisation of existing atherosclerotic plaques [11]. It must be emphasised that a systemic inflammatory response measured by elevation of C-reactive protein and interleukin-6 levels has been shown to be associated with worse prognosis in patients with unstable angina and MI [22, 23]. Long-term outcome in COPD patients may also be affected by decreased likelihood of cardiac rehabilitation attendance after MI [24].

Several important limitations of the present report should be acknowledged. First of all, the study has all the limitations of a registry. Secondly, according to the purpose of the analysis, the study focused only on in-hospital clinical outcomes of patients treated conservatively in centres without on-site invasive facilities. Data concerning mortality in the group of patients transferred for invasive treatment, as well as long-term clinical follow-up data for all patients, were not available. The most important limitation of the study is that COPD was diagnosed based on local physician assessment only and no pulmonary function testing to confirm the diagnosis was performed. This may lead to underestimation of COPD frequency, but similar methods to define COPD were used in the previous studies [2, 4]. On the other hand, patients with chronic heart failure presenting with dyspnoea may be incorrectly classified as COPD patients. Also, we were unable to classify the COPD severity, and it is probable that the relative impact of COPD on outcome is dependent on disease severity. However, the observed associations between COPD diagnosis and in-hospital management and mortality are clinically important.

In conclusion, coexistence of COPD in patients with acute MI may be associated with less frequent transfer for invasive treatment, less aggressive pharmacotherapy, and higher in-hospital mortality in patients remaining in community hospitals without on-site invasive facilities. These differences may be partially driven by a higher risk profile of COPD patients.

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# Związek pomiędzy współistniejącą przewlekłą obturacyjną chorobą płuc a rokowaniem wewnątrzszpitalnym u pacjentów z ostrym zawałem serca

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## Streszczenie

**Wstęp:** Współistnienie przewlekłej obturacyjnej choroby płuc (COPD) u pacjentów z chorobą niedokrwienną serca poddawanych zabiegom przezskórnej interwencji wieńcowej jest związane z niekorzystnym rokowaniem krótko- i długoterminowym.

**Cel:** Ocena zależności pomiędzy obecnością COPD a postępowaniem leczniczym i śmiertelnością wewnątrzszpitalną u pacjentów z ostrym zawałem serca przyjmowanych do szpitali bez pracowni hemodynamiki.

**Metody:** W Małopolskim Rejestrze Ostrego Zespołu Wieńcowych w okresach od lutego do marca 2005 r. oraz od grudnia 2005 do stycznia 2006 r. wśród chorych z rozpoznaniem ostrego zawału serca było 81 (11,3%) pacjentów z COPD i 633 (88,7%) pacjentów bez COPD. Oceniono dane dotyczące postępowania leczniczego i śmiertelności w okresie hospitalizacji.

**Wyniki:** Pacjenci z COPD byli starsi, częściej stwierdzano u nich wcześniejsze objawy dusznicowe, objawy niewydolności krążenia, przebyty udar mózgu i obniżoną kurczliwość lewej komory serca. Rzadziej byli oni przekazywani do leczenia inwazyjnego [COPD (-) vs COPD (+), 12,3 vs 34,9%,  $p < 0,0001$ ] oraz rzadziej otrzymywali kwas acetylosalicylowy i klopidogrel w okresie hospitalizacji. Śmiertelność wewnątrzszpitalna była wyższa wśród pacjentów z rozpoznaniem COPD [COPD (-) vs COPD (+), 58 z 412 (14,1%) vs 21 z 71 (29,6%),  $p = 0,002$ ]. W analizie wieloczynnikowej regresji Coksa COPD była niezależnym czynnikiem ryzyka wystąpienia zgonu w okresie hospitalizacji.

**Wnioski:** U chorych z ostrym zawałem serca współistnienie COPD może być związane z rzadszym podejmowaniem diagnostyki inwazyjnej, mniej agresywnym leczeniem farmakologicznym oraz wyższą śmiertelnością wewnątrzszpitalną wśród pacjentów pozostających w szpitalach bez pracowni hemodynamiki. Obserwowane różnice mogą być częściowo związane z wysokim ryzykiem pacjentów z COPD.

**Słowa kluczowe:** przewlekła obturacyjna choroba płuc, zawał mięśnia sercowego, leczenie, śmiertelność

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