







Comorbidities and clinical outcomes of a lung cancer screening trial participants with chronic obstructive pulmonary disease in three-year follow-up

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Abstract

Background: To improve the effectiveness of lung cancer screening using low-dose computed tomography (LDCT), the presence of smoking-related comorbidities that may significantly affect mortality in this group should be taken into account. **Material and methods:** A questionnaire survey and spirometry tests were conducted in a group of 730 respondents as part of a lung cancer screening study between 2016 and 2018. People diagnosed with COPD underwent a three-year follow-up to assess the incidence of medical events. **Results:** Our study confirmed that cardiovascular diseases (CVDs) were the most common comorbidities in patients who were diagnosed with COPD and participated in LDCT lung cancer screening. Among the CVDs, the most common were arterial hypertension (45.8%) and coronary artery disease (12.5%). Tobacco-related diseases (e.g. CVD, lung cancer, and exacerbations of COPD) were the leading causes of emergency department visits and hospitalizations. The number of visits due to COPD in specialized clinics more than doubled in the observed period. **Conclusions:** Properly planned screening tests allow not only for the detection of the disease for which they were designed but also for the assessment of comorbidities. In patients undergoing lung cancer screening, it is justified to extend the diagnostics to include spirometry.

Keywords: chronic obstructive pulmonary disease • diagnostic radiology • oncology • lung cancer • respiratory tract • screening

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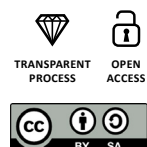
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Introduction

Chronic obstructive pulmonary disease (COPD) is a major health problem worldwide [1]. According to the World Health Organization (WHO), it is the third leading cause of death after coronary artery disease and stroke [2]. The most significant risk factor for COPD is exposure to tobacco smoke [3]. Changes caused by harmful gases and particles lead not only to local inflammatory processes in the airways, but also to systemic inflammation responsible for the considerable comorbidities found in COPD patients [3-5]. According to available data, individuals with COPD have a five-fold higher risk of developing cardiovascular diseases and a two-fold risk of lung cancer compared with smokers without COPD [6-8].

Data from randomized trials targeting the smoking population shows that low-dose computed tomographic (LDCT) screening, through secondary prevention, reduces lung cancer mortality in this group [9-11]. To improve the effectiveness of LDCT screening, trials assessing the potential benefits of combined oncological-pulmonary screening have been conducted in many countries [12-14]. In Poland, there is still not enough epidemiological data about the prevalence of COPD [4]. There is a significant need to assess the impact of lung cancer comorbidities on LDCT screening effectiveness. Therefore, after lung cancer screening programmes, observational studies on medical outcomes of participants are conducted. In this article, we present the data from a three-year follow-up of Polish LDCT screening trial participants in whom complete spirometry was performed to detect COPD.

Patients and methods

To establish the prevalence of main tobacco-related comorbidities among participants of the lung cancer screening program "MOLTEST-BIS: Validation of molecular signatures of early lung cancer in the high-risk group", started in 2016 [15], we conducted an additional investigation to assess the prevalence of COPD. The eligibility criteria were based on the lung cancer screening trial criteria were as follows: aged 50 to 79 years, citizens of Pomeranian Voivodeship, with a smoking history of over 30 pack-years, and either current or former smokers (but only those who had quit smoking no more than 15 years before the screening). Patients provided written

informed consent to participate in the study. The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (approval No NKBBN/173/2016).

Standardized questionnaire surveys that included questions about the patients' medical histories, previous diseases, medications, smoking histories and respiratory symptoms were distributed. All participants then underwent physical examination and spirometry with a bronchodilator reversibility test.

We established the prevalence and staging of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (3). We also assessed the impact of the disease on quality of life and published that analysis separately [16]. All participants diagnosed with COPD were informed about their spirometry results and the necessity of specialized pulmonary care to implement appropriate treatment. They underwent a three-year follow-up observational study.

In cooperation with the Agency for Health Technology Assessment and Tariff System (AOTMiT) and according to the agreement with the Medical University of Gdańsk, we performed an assessment of participants' main causes of death, hospitalizations and number of COPD-related visits in specialized healthcare centers until the end of 2020. The analyses were performed based on the International Classification of Diseases, Tenth Revision (ICD-10) coded data from Statistics Poland (Główny Urząd Statystyczny).

Patients were identified in the National Health Fund database, which is implemented in the AOTMiT's data archive system. Episodes of hospitalizations, outpatient specialist care and basic medical care (with the main ICD-10 codes) from the period of two years before and three years after the date of examination in the screening trial were arranged chronologically. Then, episodes of visits and hospitalizations by main disease were summarized at six-month intervals, starting from the date of examination. As a result, the number of visits and hospitalizations was presented in the six-month interval periods before and after the date of the study. A different scenario was applied to summarize the number of patients, which was counted incrementally starting from the date of examination in the screening trial. A period of six months was applied, thus the number of patients was presented in six-month follow-up intervals as well as in six-month period intervals before the date of the study. Descriptive statistics were used to summarize and present the data.

Results

The records of 730 participants (335 women and 395 men) from the lung cancer screening program MOLTEST-BIS were analyzed. The mean age of the men and women participating in the study was similar (63.5 vs 63). Based on spirometry results before and after bronchodilator administration, 144 COPD cases (19.7%) were diagnosed (86 men and 58 women). Most cases detected were in the mild stage of the disease, according to the GOLD classification. These results are presented more precisely in a separate article [16].

Table 1 presents the data on the main comorbidities among COPD patients at the beginning of the programme. Comorbidities were recorded based on the questionnaire data. The most common chronic disease reported by the participants was hypertension (45.8%), followed by coronary artery disease (12.5%), diabetes (11.8%) and atrial fibrillation (10.5%). Asthma was reported by 9.7% of the respondents, which required a differential diagnosis with COPD.

The mean duration of follow-up after the screening was 44 months (SD 8.3). We assessed the main causes of death, hospitalizations and visits to specialized healthcare centers among all respondents with COPD diagnoses. Five deaths

Table 1. Illnesses coexisting with COPD

	COPD (N = 144)
Hypertension	66 (45.8%)
Coronary artery disease	18 (12.5%)
Diabetes	17 (11.8%)
Atrial fibrillation	15 (10.5%)
Bronchial asthma	14 (9.7%)
Neoplasm (excluding lung cancer)	11 (7.6%)
Atherosclerosis of lower extremities	11 (7.7%)
Valvular heart disease	10 (6.9%)
Myocardial infarction	7 (4.9%)
Stroke	5 (3.5%)
Atherosclerosis of carotid arteries	4 (2.8%)
Renal failure	3 (2.1%)
Aortic aneurysm	2 (1.4%)

were reported during the follow-up period. Causes of death according to the ICD-10 code and the most common causes of visits to the Emergency Departments (ED) during three-year observation are presented in Tables 2 and 3, respectively. Most commonly, patients were admitted to the ED due to cardiovascular diseases (CVD), particularly atrial fibrillation (I48) and hypertension (I10). The next most common causes of patients' visits to the ED were lung cancer (C34) and COPD (J44). Additionally, one hospitalization was coded as dyspnoea

Table 2. Causes of death according to ICD-10

	ICD
Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	I63.5
Atherosclerotic cardiovascular disease	I25.0
Bacterial pneumonia, not specified	J15.9
Malignant neoplasm of overlapping sites of oesophagus	C15.8
Malignant neoplasm of overlapping sites of bronchus and lung	C34.8

Table 3. Causes of visits to the Emergency Department (ED)

	Visits to ED (N = 110)	ICD-10
Cardiovascular diseases	34/110 (31%)	
• Atrial fibrillation	11 (10%)	I48
• Hypertension	10 (9.0%)	I10
• Chest pain	6 (5.4%)	R07
• Atherosclerotic cardiovascular disease	2 (1.8%)	I25
• Palpitations	2 (1.8%)	R00.2
• Observation for suspected myocardial infarction	2 (1.8%)	Z03.4
• Stroke	1 (0.9%)	I63
Lung cancer	16/110 (14.5%)	C34
COPD	12/110 (11%)	J44
Others	46/110 (42%)	

(R06) and another as a different respiratory disorder (J98). Other causes of visits to the ED were reported very rarely.

Table 4 presents the most common causes of hospital admissions. The most common cause of hospitalization was cataracts (17.6%, ICD codes H25 and H26). Additionally, 12.2% of hospitalizations were due to CVD, 7.5% were due to lung cancer and almost 5% were related to COPD. Other causes of hospitalization occurred sporadically and thus have not been analyzed.

Table 5 shows the number of visits to specialized health-care centers related to COPD before and after the screening

program in semi-annual periods. The total number of visits within three years of follow-up was 3384. A two-fold increase in the number of visits related to COPD was found after the screening. There were 95 visits during the two-year pre-screening observation, compared with 212 visits in two years of follow-up and 300 in three years of follow-up.

Discussion

In many research centers, additional attempts have been made to assess the prevalence of COPD during lung cancer screening programs. These data are heterogeneous and depend on the diagnostic criteria and individual characteristics of the studied population [16]. The prevalence of COPD among participants of lung cancer screening is reported to be as high as 60% [17-18]. In the Polish lung cancer screening program, MOLTEST-BIS, the prevalence of COPD was almost 20% [27]. According to National Lung Screening Trial (NLST) data, mortality from lung cancer, cardiovascular diseases and respiratory failure among patients with COPD in USA increases with the increasing severity of the disease [19]. COPD is a known risk factor for CVD and lung cancer, independent of smoking status [7]. Moreover, patients with COPD tend to have a longer duration of hospitalization and an increased risk of 30-day mortality after myocardial infarction, exacerbations of heart failure and cardiac or surgical procedures [7, 20-21]. To achieve the highest effectiveness of lung cancer screening, it is recommended to pay special attention to participants with coexisting COPD [12, 19, 22-23]. According to epidemiological

Table 4. Causes of hospital admissions

	Hospital admissions (N = 204)	ICD-10
Cataract	36/204 (17.6%)	H25-26
Cardiovascular diseases	25/204 (12.2%)	
• Atherosclerotic cardiovascular disease	12	I25
• Atrial fibrillation	4	I48
• Stroke	3	I63
• Myocardial infarction	2	I21
• Hypertension	2	I10
• Cardiac arrest	1	I46
• Pulmonary embolism	1	I26
Lung cancer	15/204 (7.3%)	C34
COPD	10/204 (4.9%)	J44
Hernia	7/204 (3.4%)	K40-44
Prostate cancer	5/204 (2.4%)	C61
Breast cancer	4/204 (1.9%)	C50
Pneumonia	3/204 (1.5%)	J15-18
Bronchitis	3/204 (1.5%)	J20
Larynx cancer	3/204 (1.5%)	C32
Others	96/204 (47%)	

Table 5. Number of visits to specialized healthcare centres

	All visits	Visits related to COPD
Before the screening trial		
4th semi-annual period	437	15
3rd semi-annual period	429	31
2nd semi-annual period	439	23
1st semi-annual period	402	26
After the screening trial		
1st semi-annual period	554	63
2nd semi-annual period	601	61
3rd semi-annual period	537	50
4th semi-annual period	552	38
5th semi-annual period	568	39
6th semi-annual period	572	49

studies conducted in Europe, CVD is the most common comorbidity associated with COPD, it concerns about 20% patients with COPD and about 9% without COPD [7, 25-26]. According to the GOLD guidelines, in mild and moderate COPD the main causes of death are lung cancer and CVD. Depending on the methodology, they constitute from 12% to 37% causes of death [27].

Our analysis confirmed that the most common comorbidities among participants with COPD were CVDs and the most common among them was hypertension [7, 24-25]. A comorbidity that required particular attention in the differential diagnosis of COPD was asthma, which was reported by 14 participants (9.7%). Due to significant tobacco exposure among these participants, the history of respiratory symptoms and data on asthma diagnosis had to be more specific to exclude the asthma-COPD overlap [3].

Patients were most often admitted to the ED due to smoking-related diseases, such as CVD, lung cancer, and COPD exacerbations, which together accounted for majority of the hospitalizations. Whereas the leading single cause of hospital admission were cataracts and we hypothesize that those could have been due to planned surgical procedures. We recorded a lower number of hospitalizations due to COPD exacerbations compared with other epidemiological studies [26]. This may be related to the early detection of COPD and the provision of feedback information to participants about the diagnosis and the necessity of the immediate start of appropriate treatment.

The effectiveness of the addition of spirometry to the lung cancer screening program was confirmed by a two-fold increase in COPD-related visits to specialized healthcare centers during follow-up (Table 5). Data obtained during the MOLTEST-BIS program indicate that modification of screening programs by implementation of new diagnostic procedures and comorbidity assessment is necessary and improves their effectiveness.

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Conclusions

Precisely planned screening programs not only allow us to diagnose a disease that they were designed for but also give us the opportunity to assess patients' comorbidities. Lung cancer screening trials are particularly important in this regard. Among the group of patients with a high burden of active and passive smoking, it is important to broaden the screening to assess the presence of COPD and comorbidities. This would allow those patients to be referred to specialized healthcare centers and receive appropriate treatment, which could prevent the progression of the disease and minimize the risk of future respiratory failure. Further studies are needed to assess the effectiveness of diagnosing and preventing COPD in this group and the possible correlation of our results with the assessment of the severity of emphysema and cardiac calcium scoring using LDCT.

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Conflicts of interests

None.

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