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Comorbidity in patients undergoing surgery for lung cancer. Do we have an adequate tool to assess it?

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Abstract

Introduction: In the recent years comorbidity has been discussed as a factor affecting therapeutic decisions, the course of treatment, and prognosis of patients with lung cancer. The aim of the study was 1. to evaluate the occurrence of comorbidities in patients with lung cancer undergoing surgery, and 2. to investigate the utility of Charlson Comorbidity Index (CCI) and Simplified Comorbidity Score (SCS) for preoperative evaluation of Polish patients with lung cancer.
Material and methods: The retrospective study included 476 patients with lung cancer, who underwent surgical treatment. In all patients, data on histopathological type of the tumor, stage, history of smoking, comorbidities, and spirometric parameters were collected. CCI and SCS scores were calculated. The presence of comorbidities was analyzed in relation to sex, histology, and stage of lung cancer. Correlations between CCI and SCS scores and age, number of pack-years, spirometric parameters were assessed.
Results: The most prevalent comorbidities were hypertension (42%), chronic obstructive pulmonary disease (COPD) (22%), coronary heart disease (17%), and diabetes (12%). There were no differences in the distribution of comorbidity depending on the histological type and stage of lung cancer. The CCI and SCS scores showed correlations with age, number of pack-years and spirometric parameters, however, their compounds do not reflect the profile of most prevalent comoribidities.
Conclusion: The burden of comorbidity among patients with lung cancer is significant. Comorbidity should be assessed while considering patients for surgical treatment. However, the CCI and SCS do not seem precise enough for this purpose.

Key words: lung cancer, comorbidity, Charlson Comorbidity Index, Simplified Comorbidity Score

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Introduction

Currently, lung cancer is the most common cause of death from neoplasms [1, 2]. The main determinants of the patient's eligibility for surgical treatment are as follows: the stage of the tumor, performance status (PS), and pulmonary function parameters. In the recent years also comorbidity has been investigated as a factor affecting the therapeutic decisions, the course of treatment, and prognosis of patients with lung cancer [3]. The problem concerns a substantial number of patients because in this population,

the risk of chronic diseases is high due to age and smoking history. It has been proven that the presence of comorbidities has an impact on the decisions of physicians qualifying patients for oncological treatment [4]. There is also evidence that comorbidity could increase the risk of adverse events during the therapy [5, 6], including surgery [6, 7]. The impact of these disorders on prognosis varies depending on the stage of lung cancer. In patients in the early stages, undergoing radical treatment, their influence on the prognosis is significant [8, 9]. In contrast, in the advanced stage of the disease, the predominant impact on

survival has lung cancer itself [10, 11]. For the purposes of the assessment before treatment, as well as in patients participating in clinical trials, the use of numerical scales quantifying comorbidities is often suggested. Currently, the most commonly used scales are Charlson Comorbidity Index (CCI) and Simplified Comorbidity Score (SCS). The CCI was developed in 1987 based on the survival analysis of 599 patients hospitalized for various medical conditions and was later validated on a group of patients with breast cancer [12]. The CCI includes a list of 19 diseases and a score they are assigned depending on their impact on mortality. The highest scores in this scale has been assigned to such diseases as AIDS, metastatic solid tumor or severe liver disease. Cardiologic problems, as well as respiratory and vascular diseases are included in common categories, and are assigned the lowest scoring [12]. The second popular scale, namely SCS is dedicated to the assessment of patients with non-small cell lung cancer. It includes 7 groups of diseases which are assigned scores depending on the impact on prognosis [13]. In this scale, in turn, the greatest negative impact on prognosis has been attributed to smoking, defined as consumption of 100 cigarettes in patient's lifetime; likewise in the CCI, cardiovascular and pulmonary diseases have a significantly lower weight.

The utility of these scales in predicting the course of treatment and outcome has been investigated. However, the results of studies on the topic are often divergent; some of them confirm the value of the CCI and SCS as prognostic indicators in patients with lung cancer [9, 13–15]. It has been shown, for example, that high scoring in both scales (CCI ≥ 3, SCS > 9) is an independent negative prognostic factor in patients with lung cancer [14]. On the contrary, studies which question their value and indicate that sufficient information is provided, for instance, by PS can also be found [10, 11, 16]. The issue of the optimal tool for the assessment of comorbidity coexisting with lung cancer still remains open. Nevertheless, due to the significant burden of chronic diseases in this group of patients, the thorough preoperative assessment of comorbidity might presumably be of importance in considering the patients for surgical treatment.

In the present cross-sectional study, our aim was to evaluate the occurrence of comorbidities in patients with lung cancer undergoing surgery and to investigate the prevalence of these diseases depending on sex, histopathological type, and stage of lung cancer. We also aimed to confront our findings with the compounds of the CCI and SCS in order to assess whether the scales can sufficiently represent comorbidity in the Polish population of patients with lung cancer.

Material and methods

Study group

The retrospective study included 476 patients (327 men and 149 women) diagnosed with lung cancer who underwent surgical treatment between January 2012 and September 2013. The inclusion criteria comprised the diagnosis of lung cancer and positive qualification for the surgical treatment. In order to perform a real-life study, we included into the study group all patients who underwent surgery for lung cancer within a given period of time. In all patients, the histopathological type of cancer and stage of the disease (TNM classification, 7th edition [17]) were evaluated. Patients were divided into three groups according to histopathology: with squamous cell carcinoma, adenocarcinoma, and other histopathological types. History of smoking (number of pack-years) and the presence of comorbidities (coronary heart disease, hypertension, myocardial infarction, peripheral vascular disease, atrial fibrillation and other arrhythmias, COPD, tuberculosis, diabetes, stroke, thyroid diseases, malignancy) were retrospectively obtained from the medical history and available medical records of the patients at the time of admission. Forced spirometry performed during the qualification for surgery was taken into account. Forced expiratory volume in one second (FEV$_1$) and vital capacity (VC) are presented as a percentage of the predicted value. In all patients, comorbidity scores were calculated according to CCI and SCS.

Methods

The presence of comorbidities was analyzed in subgroups according to sex, histology of the tumor and stage of lung cancer. Correlations between CCI, SCS scores and age, number of pack-years, spirometric parameters were assessed, depending on gender, histopathological type, and the stage of cancer. Scoring in the CCI and SCS was analyzed as a continuous and dichotomous variable (for the CCI scores < 3 and ≥ 3 and for the SCS scores ≤ 9 and > 9 [14]). Quantitative variables are presented with the following descriptive statistics: mean (range, SD) or median (IQR) for variables with non-Gaussian distribution, and the variable quality on a numbers (n) and percentages. For the quantitative variables compliance

with a normal distribution was tested using the Shapiro-Wilk test. The homogeneity of variance was examined by the Kolmogorov-Smirnov test. To examine differences between groups for quantitative variables with Gaussian distribution and homogeneous variance Student's t test was used. With non-gaussian distribution or non-homogenous variance Mann-Whitney U test was used. To examine the relationship between variables of gaussian distribution Pearson's test was usted. In the case where one of the variables had non-gaussian distribution, Spearman test was used. To examine differences between groups using qualitative variables Pearson Chi^2 test was used. Cluster analysis was performed by k-means. The level of significance was set at $p = 0.05$. Statistical analyzes were performed using Statistica 10.0. For this type of study (retrospective study) formal consent of the ethics review board is not required.

Results

Statistics of the study group

A group of 476 patients operated for lung cancer (327 men, 149 women) was evaluated. The mean age was 63.7 (min 22, max 84; SD 7,9). About 94% of the group were smokers (current or former) and 6% nonsmokers. The mean number of pack-years was 45.5 min 0, max 138; SD 22,25); there was a statistically significant difference between men and women in the number of pack-years (women: mean 34,72, 0-102, SD 17,8; men: mean 50,06, 0-138, SD 22,4; U Mann-Whitney test $p = 0.000$).

Spirometric parameters (FEV_1, VC) were analyzed as percent of the predicted value. In the total group the mean FEV_1 was 83% and the mean VC was 93%. In men the mean values were as follows: FEV_1 82%, VC 89%; in women 85% and 101%, respectively. The differences of VC between men and woman appeared statistically significant (*U* Mann-Whitney test $p = 0.01$). The mean FEV_1 in patients with squamous cell carcinoma was slightly lower (80%) than in patients with adenocarcinoma (86%) and other histopathological types (85%). The same regularity was related to VC (91% vs 94% and 94%), but the differences were not found statistically significant.

Patients with squamous cell carcinoma comprised 45% of the group (n = 215), with adenocarcinoma 40% (n = 190), the other histopathological types 15% (n = 71). The other histopatological types of tumors are summed up in the table (Table 1). There were no significant differences in the distribution of histological types between men and women.

Table 1. Histopathological diagnoses grouped as "other histopathological types"

Other histopathological types of tumors	n	%
Large cell carcinoma	21	4
Carcinoid (typical and atypical)	13	3
Bronchioloalveolar carcinoma	9	2
Non-small cell carcinoma (not otherwise specified, NOS)	7	1
Small cell carcinoma	5	1
pleomorphic carcinoma	4	1
Sarcomatoid carcinoma	3	0,5
Neuroendocrine carcinoma	3	0,5
Adenosquamous carcinoma	1	< 0,1
Basaloid carcinoma	1	< 0,1
Spindle cell carcinoma	1	< 0,1
Carcinoma adenoides cysticum	1	< 0,1

Detailed data of the study group are summarized in Table 2.

The occurrence of comorbidities

In the study group, the most prevalent comorbidities were as follows: hypertension (42% of patients), COPD (22%), coronary heart disease (17%), and diabetes (12%). Some statistically significant differences in the prevalence of certain comorbidities between women and men were observed. In women, thyroid diseases were more frequent (15% vs. 2%, Pearson Chi^2 $p < 0.05$), while in men, peripheral arterial disease (10% vs. 4%, Pearson Chi^2 $p < 0.05$) and myocardial infarction (12% vs. 5%, Pearson Chi^2 $p < 0.05$) were found more prevalent. In the whole study group, hypertension was the most common comorbid disease in both genders, in patients at all stages of cancer, and in all histopathological types ($p < 0.05$) (Figs 1, 2).

The analysis of comorbidities depending on the histological type of lung cancer showed no statistically significant differences; however, some trends were apparent for more frequent occurrence of certain diseases. For example, COPD was slightly more common in patients with squamous cell carcinoma (Pearson Chi^2 $p = 0.07$) (Fig. 2).

There were no differences in the distribution of comorbidities depending on the stage of lung cancer.

To determine the distribution of comorbidities in the study group, cluster analysis by k-means has been conducted. We eliminated from the cluster analysis the comorbidities that occurred least often or have not affected the
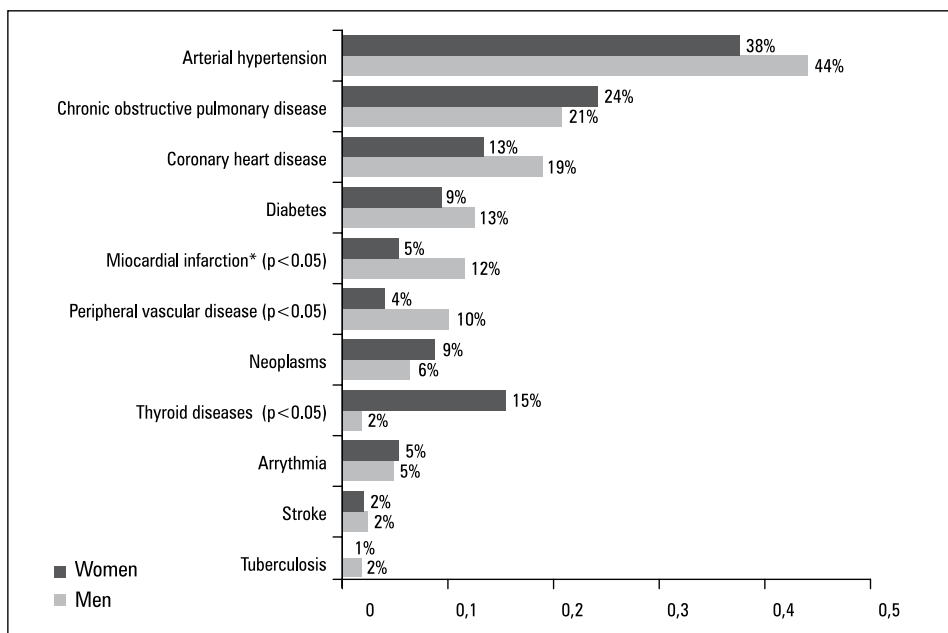
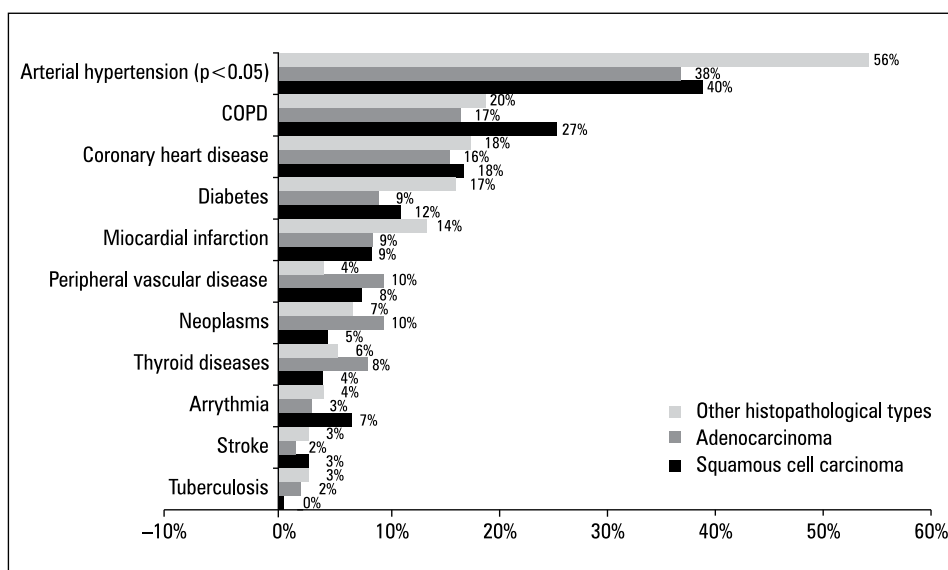**Figure 1.** The presence of comorbidities depending on gender

Figure 2. The presence of comorbidities depending on the histopathological type of tumor

differences between the clusters. The analysis included the following diseases: hypertension (HTN), COPD, coronary heart disease (CHD), myocardial infarction (MI), peripheral vascular disease (PVD) and diabetes mellitus (DM). Two clusters of patients appeared, which differed in the incidence of cardiovascular diseases and diabetes. The cluster 1 comprised 365 patients, and the cluster 2 comprised 111 patients. The occurrence of comorbid diseases in both clusters is shown on the graph (Fig. 3). The incidence of COPD in both groups was similar, which can be related to dominance of smokers in the study group. The clusters have been compared in terms of gender, age, histological diagnosis and history of smoking. Patients in the cluster 2, in which the incidence of cardiac disease and diabetes was higher, were older than patients in cluster 1 ($p < 0.05$). The mean age of patients in the cluster 1 was 62.7 (22–83, SD = 8.01), in the cluster 2 66.7 (51–84, SD = 6.88). There were no differences in terms of gender, histopathological diagnoses and the number of pack-years.
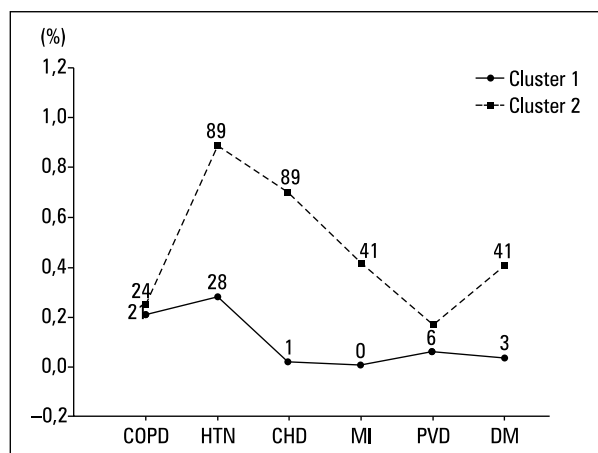
Figure 3. Cluster analysis of the prevalence of comorbidities in the study group. The prevalence of the comorbid diseases is presented as percentages. COPD — chronic obstructive pulmonary disease; HTN — arterial hypertension; CHD — coronary heart disease; MI — myocardial infarction; PVD — peripheral vascular disease; DM — diabetes mellitus

Evaluation of CCI and SCS scores

CCI

In the whole study group, the median CCI score was 0 (IQR 0-1). There were no significant differences between men and women. In the entire group, there was a statistically significant positive correlation of the CCI score with age and the number of pack-years and a negative correlation with spirometric parameters (VC, FEV1) (Spearman's rank correlation, $p < 0.05$) (Table 3).

About 6.7% of the study group (n = 32) achieved a CCI score $\geq$ 3. This group of patients had a significantly higher number of pack-years history (mean 53.8, 0-126; SD 27.1) compared to patients with the CCI < 3 (mean 44.7; 0-138; SD 21.6) (U Mann-Whitney test, $p < 0.05$), without any differences in terms of age and spirometric parameters. There were no differences between men and women when it comes to the distribution of CCI scores < 3 and $\geq$ 3. Moreover, no association could be observed between the tumor stage or histopathological type and the CCI score.

SCS

The median SCS score was 8 (IQR 7–9). In the whole study group, there was a statistically significant positive correlation of SCS score with age and the number of pack-years and a negative correlation with spirometric parameters (Spearman's rank test, $p < 0.05$). There was a significant difference between the SCS scores in men and woman (U Mann-Whitney test, $p = 0.01$).

About 12.1% of the study group (n = 58) achieved an SCS score >9. Patients in this group were

Table 2. Characteristics of the study group. Statistically significant differences between subgroups are marked with *U* Mann-Whitney test

Characteristics of the study group	n	%
Population	476	100
women	149	31
men	327	69
Histopathological type of cancer		
squamous cell carcinoma	215	45
adenocarcinoma	190	40
other histopathological types	71	15
Stage of lung cancer (TNM, 7th edition)		
IA	71	15
IB	97	21
IIA	111	24
IIB	49	10
IIIA	112	24
IIIB, IV	28	6
Smoking history		
current or former smokers	448	94
non-smokers	28	6

	Mean	Range	SD
Age			
total group	63.70	22–84	7.9
women	63.60	22–77	7.6
men	63.74	29–84	8.1
Number of pack-years			
total group	45.5	0–138	22.25
women	**34.92***	**0–102***	**17.8***
men	**50.06***	**0–138***	**22.4***
squamous cell carcinoma	48.39	0–138	22.7
adenocarcinoma	44.53	0–120	22.7
other histopathological types	38.64	0–86	20.19
Spirometric parameters FEV₁ (% pred.)			
total group	83		
women	85		
men	82		
squamous cell carcinoma	80		
adenocarcinoma	86		
other histopathological types	85		
VC (% pred)			
total group	93		
women	**101***		
men	**89***		
squamous cell carcinoma	91		
adenocarcinoma	94		
other histopathological types	94		

*$p < 0.05$

older and were characterised by worse spirometric parameters compared to the group of SCS $\leq$ 9 (U Mann-Whitney test $p < 0.05$), while there was no significant difference when it comes to the history of smoking. There were no differences between men and women in distribution of SCS scores $\leq$ 9 and

Table 3. Correlations coefficients between scores in the CCI and SCS, and patients' age, number of pack-years and spirometric parameters

	CCI			SCS		
	test	r	p	test	r	p
Age	Spearman's rank correlation	0.17	0.0001	Spearman's rank correlation	0.19	0.000
VC (% pred)	Spearman's rank correlation	–0.16	0.0005	Spearman's rank correlation	–0.16	0.000
FEV_1 (% pred)	Spearman's rank correlation	–0.20	0.000	Spearman's rank correlation	–0.16	0.000
Number of pack-years	Spearman's rank correlation	0.10	0.0397	Spearman's rank correlation	0.16	0.0007

p < 0.05 was considered statistically significant; CCI — Charlson Comorbidity Index; SCS — Simplified Comorbidity Score; FEV_1 — forced expiratory volume in one second; VC — vital capacity

Table 4. Evaluation of the study group in the CCI and SCS. CCI and SCS are presented as medians (IQR). Age and pack-years are presented as means (range, SD). FEV_1 and VC are presented as mean percentages. Statistically significant differences between subgroups are marked with *U* Mann-Whitney test

Evaluation of the study group in the CCI and SCS		
Scoring in the scales	CCI (median, IQR)	SCS (median, IQR)
Total group	0 (0–1)	8 (7–9)
women	0 (0–1)	8 (7–9)
men	0 (0–1)	8 (7–9)
Squamous cell carcinoma	1 (0–1)	8 (7–9)
Adenocarcinoma	0 (0–1)	8 (7–8)
Other histopathological types	1 (0–1)	8 (7–9)
Characteristics of subgroups according to CCI scoring	CCI < 3 (n = 444) (mean, range, SD)	CCI ≥ 3 (n = 32) (mean, range, SD)
Age	63.66 (22–84; 8.03)	64 (52–77; 6.71)
Pack-years	**44.7 (0–138; 21.6)***	**53.8 (0–126; 27.1)***
FEV_1 (% pred)	83%	83%
VC (% pred)	93%	90%
Characteristics of subgroups according to SCS scoring	SCS ≤ 9 (n = 418) (mean, range, SD)	SCS > 9 (n = 58) (mean, range, SD)
Age	**63.27 (22–83; 8.03)***	**66.79 (55–84; 6.52)***
Pack-years	44.8 (0–138; 22.5)	50.2 (10–117; 19.9)
FEV_1 (% pred)	83%	80%
VC (% pred)	**93%***	**88%***

*p < 0.05; CCI — Charlson Comorbidity Index; SCS — Simplified Comorbidity Score; FEV_1 — forced expiratory volume in one second; VC — vital capacity

> 9. Likewise, no association was found between tumor stage or histopathological type and the SCS score.

Details of the CCI and SCS assessment are shown in Tables 3 and 4.

To sum up the characteristics of the two groups with the highest burden of comorbidity according to the CCI and SCS, we found that patients with the CCI score ≥ 3 were characterised by a higher number of pack-years than patients with CCI < 3, and patients with the SCS score > 9 were older and had worse spirometric parameters than patients with the SCS ≤ 9.

Discussion

In the current study, we attempted to describe a group of patients operated for lung cancer in terms of incidence of comorbidities. Moreover, our aim was to assess some commonly used numerical scales quantifying chronic diseases for their suitability for preoperative assessment of patients with lung cancer. We analysed a large group of patients scheduled for surgery (n = 476), which is comparable to previous data regarding Polish patients with lung cancer in terms of age and history of smoking [18]. Pa-

tients in the early stages of cancer dominated in the study group, which is understandable in the context of the planned radical surgical treatment. Patients in stages IIIB and IV accounted for a total of 6%, which is a result of intraoperative re-staging.

While considering surgery in patients with lung cancer, a number of factors characterising the patient, including stage of the tumour, PS, and lung function parameters, are usually taken into account [19, 20]. Patients with lung cancer, mostly elderly people and heavy smokers, are at particular risk of chronic diseases. This can be seen in the study group in which high proportion of current or former smokers (94%) and high average number of pack-years (45.5) translates into a high prevalence of tobacco-related diseases. Indeed, the most prevalent disorders observed in our study (hypertension, COPD) occur more frequently than it has been reported for the Polish population (respectively, 42% vs. 29% [21], 22% vs. 10% [22, 23]. It has been observed that these diseases as tobacco-related disorders, tend to coexist [24]. Some differences in the occurrence of comorbidity between men and women were also shown (e.g., higher incidence of myocardial infarction and peripheral arterial disease in men), which may be associated with a significantly higher number of pack-years in men. Differences in the coexistence of various histological types of lung cancer and chronic diseases were insignificant. Higher incidence of COPD in patients with squamous cell carcinoma can be attributed to a particularly strong association of this histological type with smoking [25]. We have also shown significantly higher incidence of cardiovascular comorbidities in older patients with lung cancer, which indicates the need for particularly careful preoperative assessment in this group of patients.

The term "comorbidity" refers to somatic and mental disorders, independent from lung cancer, which may affect the safety of the treatment and outcome. It should be distinguished from the term "performance status" (PS), most widely used in oncology, describing the patient's ability to perform daily activities. The low PS may result from both the cancer itself and comorbidity; however, it has been proven that these traits should be considered independently [26]. Moreover, the assessment of PS by a physician is highly subjective. In this analysis, the PS is not included because the examined patients were characterized by high PS (0–1), and therefore this parameter did not give any additional information.

For numerical description of comorbidity, two most widely used scales were applied: CCI and SCS. Correlations between scores in these scales and patients' age, history of smoking, and deterioration of spirometric parameters were observed. To sum up the evaluation of the study group in the CCI and SCS, we can say that the highest scores obtained in the examined scales applies to elderly patients, with worse spirometric parameters and heavy smokers. However, no correlation was found between the burden of comorbidities and the stage of lung cancer or histopathological type.

Opinions on the prognostic value of the CCI and SCS vary [9–11, 13–16]. The scales differ significantly in terms of their components and the weight each component of the scale is assigned. Currently, the CCI is used most widely. Note, however, that this scale has been used for nearly 30 years, and the impact of its individual components on the prognosis has changed during this time concurrently with the progress of diagnostics and therapy of particular conditions comprising the scale (an example might be AIDS, which is assigned the highest score in the scale). Similarly, the SCS puts the greatest emphasis on to smoking which is defined as consumption of 100 cigarettes in the patient's lifetime [13] and which seems out of proportion to much lower scoring of cardiovascular or respiratory diseases. From the standpoint of the clinician qualifying patients for surgery, the high incidence of COPD and cardiovascular diseases observed in our study seems to be essential. Globally increasing mortality due to COPD is well known [27]. It has been also proven that the occurrence of this single disease adversely affected prognosis of patients operated for lung cancer [28]. Similarly, the coexistence of cardiovascular disease has been associated with a higher rate of postoperative complications in such patients [29, 30]. However, in both CCI and SCS these diseases are of minor importance and their impact on prognosis is marginalised. Moreover, hypertension, a condition most commonly observed in our study group is not considered in the CCI at all. It seems, therefore, that the use of these scales, at least for the contemporary Polish population of patients with lung cancer may lead to underestimation of operational risk associated with the occurrence of respiratory an cardiovascular diseases. In other cases the use of these scales may result in assigning an excessive risk, for example in patients with a history of smoking but without significant tobacco-related diseases, assessed in the SCS. Thus, although

consideration of chronic diseases in preoperative assessment of patients with lung cancer appears to be reasonable, in our opinion the CCI and SCS do not seem sufficient for this purpose.

A limitation of the present study is the lack of information about the long-term survival of the study group, due to the retrospective character of the study and lack of follow-up information. Further studies on the impact of comorbidities on survival of patients with lung cancer are necessary, especially as the data for the Polish population on the topic are scarce.

Conclusions

In conclusion, the present study revealed a significant burden of comorbidity among patients with lung cancer, higher than in the general population. Thus, comorbidity should be assessed while considering this group of patients for surgical treatment. Scoring in two popular scales quantifying comorbidity, CCI and SCS, correlates with some patients' characteristics commonly considered by physicians, such as age, smoking history and spirometric parameters. However, the CCI and SCS scales do not reflect the profile of comorbidity in patients with lung cancer sufficiently, and therefore do not seem precise enough for this purpose.

Conflict of interest

The authors declare no conflict of interest.

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