

## Worse Prognosis in the Symptomatic Patients With Lung Cancer – Czech Multicentric Study

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**Abstract.** *Background/Aim:* This study aimed at contributing to a better diagnosis of lung cancer by analyzing the patient's symptoms and their linkage to other characteristics. *Patients and Methods:* We analyzed the data of 3,322 patients from LUCAS (LUNgCAnceRfocuS) National Registry of the Czech Republic. Overall survival was assessed using the Kaplan–Meier method. *Results:* The most common symptoms were cough (47.5%), dyspnea (45.6%), pain (27.3%), and weight loss (25.7%). Among all patients, 16% were asymptomatic. We

demonstrated the negative prognostic significance of increasing number of lung cancer symptoms, that was significant after adjustment for age, TNM stages, and performance status, and morphological types of the cancer. *Conclusion:* Monitoring the severity and type of symptoms in patients with lung cancer can help in the diagnostics of the disease and the estimation of prognosis.

According to the Institute of Health Information and Statistics (IHIS), only 20% of patients were diagnosed with TNM (8<sup>th</sup> edition of the UICC TNM Classification) stage I and II between 2014 and 2018. Those in TNM stage III and IV accounted for 80% (1). These patients usually show symptomatic disease at the time of diagnosis and a worse prognosis. Some symptoms, especially hemoptysis, can also be a guide for the diagnosis of lung cancer (2). It is also known that some clinicopathological characteristics may correlate with certain symptoms or even with their severity (3). In this respect, however, we believe that it would be more appropriate to describe lung cancer as a whole, whereas the latter study dealt only with adenocarcinomas. The possible relationship of some of these lung cancer

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symptoms with the poorer prognosis of patients is also described (4, 5). However, the Spanish study included only 267 patients, and the British study refers to patients from earlier years and a limited number of institutions. For these reasons, we performed this multicenter study with prospectively collected data that reflects patients from a recent time period and thus with modern therapies. The aim of this report was to describe the symptoms of patients with lung cancer in the Czech Republic on the basis of the (LUCAS-LUngCAnCERfocuS) national registry as well as present their correlation to basic clinicopathological data and assess their possible prognostic significance.

### Patients and Methods

**Study design.** The LUCAS registry is a project of the Czech Pneumology and Phthizeology Society. The project is registered at ClinicalTrials.gov under the registration number NCT 04228237. Seven pulmonary-oncology centers in the Czech Republic have been prospectively registering and monitoring all consecutive patients diagnosed and treated with lung cancer since June 1, 2018. For each patient, the basic characteristics (weight, age), smoking habits, symptoms at the time of diagnosis, morphological verification, tumor location, TNM stage, genetic tests of biomarkers, and positivity of PD-L1 tests, as well as type and results of treatment are recorded.

Data from 3,322 patients in the LUCAS registry with date of diagnosis and complete data on the occurrence of symptoms were used to analyze symptoms in patients with lung cancer. The project was approved by the Ethics Committee of Palacky University in Olomouc on June 11, 2018, under reference number 63/18 MEK 13. All patients signed an informed consent to enroll in the study.

**Statistical methods.** Quantitative data are described using the Valid N (number of patients with value filled in), the mean (SD, standard deviation) and the median (of the 5th and 95th percentiles). Categorical parameters are described by absolute and relative frequencies calculated from the filled-in data. Differences in quantitative parameters between two groups were tested using the Mann–Whitney *U*-test, whereas differences between three groups were examined using the Kruskal–Wallis *H* test. Differences between categorical parameters were tested using Pearson’s chi-squared test.

Overall survival (OS) was assessed using the Kaplan–Meier method, where all the point estimates were complemented with 95% confidence intervals. The OS was determined as the time from diagnosis to the patient’s death (for whatever reason). Patients who did not reach the OS value at the time of the set evaluation (July 2021) were censored as at the date of their last known appointment. Statistical significance for the OS was assessed using the log-rank test. The analysis of risk factors was performed using the Cox proportional hazards regression model (one-dimensional and multidimensional regression). Within the multidimensional regression, the categories of the symptoms number were adjusted by age, disease stage, performance status (PS) and tumor type.

Hypothesis testing was performed at the 5% significance level. The analysis was performed using the IBM SPSS Statistics 24 software (IBM, New York, USA).

Table I. *Baseline patient characteristics (percentages for each variable are calculated from the data entered in the LUCAS register).*

Parameter	n (%)
Gender	
Male	2,016 (61%)
Female	1,306 (39%)
Smoking status	
Smokers	1,712 (53%)
Ex-smokers	1,103 (34%)
Non-smoker	408 (13%)
ECOG PS	
0	710 (23%)
1	1,717 (54%)
2	532 (17%)
3	198 (6%)
Histology	
Adenocarcinoma	1,342 (43%)
Squamous cell carcinoma	927 (29%)
Small cell carcinoma	525 (17%)
NSCLC-NOS	364 (11%)
Stage	
I	358 (11%)
II	270 (8%)
III	860 (27%)
IV	1,718 (54%)

ECOG PS: Eastern Cooperative Oncology Group performance status; NSCLC-NOS: non-small cell lung cancer not otherwise specified.

### Results

**Basic patient characteristics.** Our analysis included data from 3,322 patients who were on average 69 years old at the time of their diagnosis. The smokers reported an average of 36.2 pack-years. Basic patients’ characteristics are summarized in Table I.

**Types and numbers of symptoms.** In the evaluated cohort of 3,322 patients, 547 were asymptomatic (16%). These patients were diagnosed incidentally while examined for other diseases, during preventive screening or screening for other diagnoses. A total of 2,775 patients (84%) exhibited symptoms that contributed to the diagnosis of lung cancer. These symptoms are presented in Table II.

The comparison of patients divided according to the number of symptoms into three groups (0 symptoms, 1-2 symptoms and 3 or more symptoms) showed that men had statistically significantly more symptoms than women ( $p=0.008$ ), and more symptoms presented patients with younger age ( $p=0.038$ ), with a higher number of pack-years of cigarettes ( $p<0.001$ ), with a lower weight ( $p<0.001$ ) and with a worse performance status (PS) ( $p<0.001$ ). The highest number of symptoms was reported in patients with the main bronchus and middle lobe involvement, whereas patients with involvement of the lower lobe had fewer symptoms ( $p<0.001$ ). Patients with NSCLC- not

otherwise specified (NOS) (3 or more symptoms in 42.6% of these patients) and with SCLC (3 or more symptoms in 42.1% of these patients) exhibited significantly more frequent symptoms than patients with adenocarcinoma (3 or more symptoms in 29.6%) ( $p<0.001$ ).

The number of symptoms was very closely related to the size of the tumor (T1 through to T4), to the involvement of lymph nodes (N0 to N3), and to the existence of metastases, and therefore to the TNM stages I through to IV ( $p<0.001$ ). Patients with TNM stage I and IV were asymptomatic at a rate of 49% and 7.1%, respectively.

Cough (exhibited in 47.5% of patients of the entire cohort) occurred equally often in men and women, but was reported more often by younger patients ( $p=0.041$ ), heavier smokers ( $p=0.001$ ), patients with lower weight ( $p=0.046$ ) and patients with poorer performance status ( $p<0.001$ ). Cough was also reported most often by patients with involvement of the main bronchus and middle lobe *vs.* other locations ( $p<0.001$ ) and, in terms of morphological types, by patients with squamous cell lung cancer (53.2%) and small cell lung cancer (48.8%), ( $p=0.002$ ). Patients reported cough in ascending order along with the tumor size, according to the extent of the involvement of intrathoracic lymph nodes, to the presence and degree of metastases, and to the TNM stage. An exception presented the patients in TNM stage IV, where cough was reported by only 50.9% of patients, whereas cough was reported by 53.5% of cases in TNM stage III ( $p<0.001$ ).

Shortness of breath was reported by 45.6% of patients of the entire cohort. There were no differences between men and women, nor between younger or older patients. Smokers reporting higher quantity of pack-years suffered from dyspnea more often ( $p=0.001$ ), as well as sick persons with poorer performance status ( $p<0.001$ ). Dyspnea was more common in patients with involvement of the main bronchus ( $p<0.001$ ), with small cell lung cancer (56%) ( $p<0.001$ ); and its incidence increased with tumor size, extent of lymph nodes involvement, existence or non-existence of metastases and with TNM stage. Furthermore, 24% of patients in TNM stage I and 50.6% in stage IV ( $p<0.001$ ) suffered from shortness of breath ( $p<0.001$ ).

Weight loss (27.5% in the entire cohort) was more common in men than in women ( $p=0.024$ ) and it was significantly more frequent in the elderly ( $p=0.001$ ), in heavier smokers ( $p<0.001$ ) and in patients with poorer performance status (PS, 2-3;  $p<0.001$ ). Patients with tumor location in the main bronchus and middle lobe reported weight loss the most frequently ( $p=0.001$ ). Patients with adenocarcinoma reported weight loss the least frequently (20.8%) ( $p<0.001$ ). Weight loss was more common in patients with larger tumors, with more extensive nodal involvement, with metastases (32.5%) *vs.* without metastases (18.6%), and increased with ascending TNM stage ( $p<0.001$ ).

Table II. *Symptoms of patients.*

Symptoms	Parameter	n (%)
Occurrence	No	547 (16.5%)
	Yes	2,775 (83.5%)
Type	Cough	1,577 (47.5%)
	Dyspnea	1,515 (45.6%)
	Pain	908 (27.3%)
	Weight loss	854 (25.7%)
	Inappetence	407 (12.3%)
	Fatigue	402 (12.1%)
	Hemoptysis	321 (9.7%)
	Febrile	186 (5.6%)
	Headache	107 (3.2%)
	Confusion	48 (1.4%)
Number	Swallowing difficulties	40 (1.2%)
	Other symptoms	347 (10.4%)
	0	547 (16.5%)
	1-2	1,613 (48.6%)
	3 and more	1,162 (35.0%)

In the entire cohort, 9.7% of patients exhibited hemoptysis. When the case histories were collected, hemoptysis was reported significantly more frequently by men than women (11.5% *vs.* 6.9%;  $p<0.001$ ), significantly more often in heavier smokers ( $p<0.001$ ) and was more common in taller and heavier patients ( $p=0.006$ ,  $p=0.001$ ). In contrast, the incidence of hemoptysis was not reported to be more frequent in patients with poor PS 2-3. Hemoptysis was significantly more common in patients with lung carcinoma in the middle lobe (14.1%) and in the main bronchus (13.7%;  $p=0.003$ ). Patients with squamous exhibited hemoptysis more frequently (15.6%) than patients with adenocarcinoma (6.6%) ( $p<0.001$ ). The incidence of hemoptysis varied significantly according to the tumor size and was most common in patients with T4. Furthermore, it progressively grew with the degree of node involvement from N0 to N2, whereas patients with N3 involvement showed hemoptysis less often than patients with N1 involvement (8.6% *vs.* 11.3%,  $p=0.009$ ). Hemoptysis was equally common in patients with M0 and M1 involvement. Occurrence of hemoptysis gradually ascended in patients from TNM stage I to stage III, but occurred in fewer patients (similarly to cough) in TNM stage IV than those in TNM stage III (9.1% *vs.* 12.8%;  $p<0.001$ ).

In the entire cohort, 5.6% of patients had fever before being diagnosed. Fever occurred in both sexes equally, although more frequently in younger ( $p<0.001$ ) and taller ( $p=0.001$ ) patients. The incidence of fevers did not vary according to the tumor location or the morphological type of cancer. The only significant difference was the higher incidence of fever in patients with N2 involvement (7.1%) compared to patients with N0, (3.3%), N1 (5.8%) and N3 (5.5%) involvement ( $p=0.011$ ).

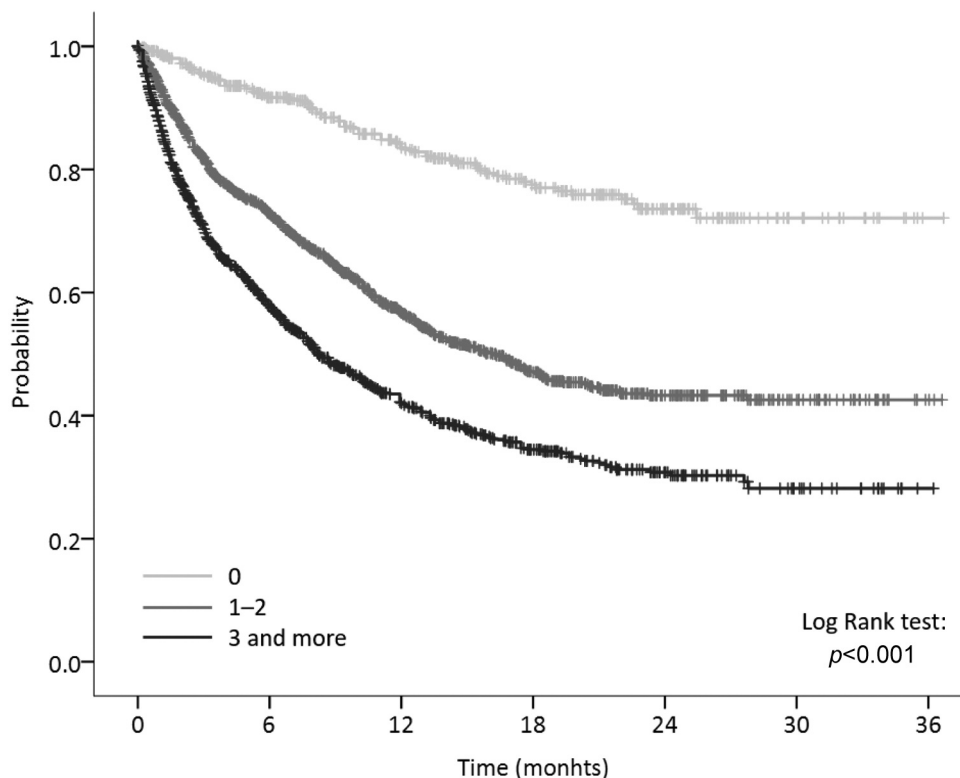


Figure 1. Kaplan–Meier curves for overall survival in relation to the number of symptoms of lung cancer.

Table III. Number of symptoms at time of diagnosis and correlation to overall survival.

Number of symptoms	Patient status		Median survival	p-Value
	Alive	Dead		
0	455 (83.2%)	92 (16.8%)	Unattained	<0.001
1-2	939 (58.2%)	674 (41.8%)	16.3 months	
3 and more	541 (46.6%)	621 (53.4%)	8.2 months	

*Symptoms of lung cancer vs. prognosis.* Finally, we present the results of the survival analysis in relation to the patients’ symptoms. As of the date of the analysis, 1387 patients (42%) of the entire cohort of 3322 individuals died. The probability of death increased with the number of symptoms at the time of diagnosis and, accordingly, the median survival decreased with the number of symptoms (Table III). Kaplan–Meier curves are shown in Figure 1.

The occurrence of symptoms significantly affected the probability of survival, even if adjusted according to age, TNM stage, PS, and morphological type of cancer (Table IV).

**Discussion**

Our study describes the symptoms of patients with lung cancer in a uniquely large group of individuals, since the Registry with its prospective inclusion of patients made it possible to focus on the linkage between these symptoms and clinical-anatomical data of patients and survival in the entire cohort. In addition to the usual description of symptoms, we can therefore put an emphasis on their prognostic significance.

Statistically significantly more symptoms occurred in men compared to women, in younger patients, in patients with

Table IV. Risk of death according to the number of symptoms, age, TNM stage, performance status and morphological type of tumor.

Parameter	HR (95%CI)	p-Value
One-dimensional model		
0	Reference group	
Number of symptoms		
1-2	3.052 (2.446-3.808)	<0.001
3 and more	4.761 (3.810-5.950)	<0.001
Adjusted model		
Number of symptoms		
0	Reference group	
1-2	1.844 (1.441-2.361)	<0.001
3 and more	2.279 (1.771-2.934)	<0.001
Age	1.012 (1.005-1.019)	<0.001
Stage		
I	Reference group	
II	1.735 (1.034-2.911)	0.037
III	3.920 (2.548-6.029)	<0.001
IV	7.907 (5.182-12.064)	<0.001
Performance status		
0	Reference group	
1	1.354 (1.138-1.612)	<0.001
2	2.888 (2.361-3.533)	<0.001
3	7.067 (5.453-9.159)	<0.001
Tumor type		
Adenocarcinoma	Reference group	
Squamous carcinoma	1.041 (0.896-1.208)	0.602
NSCLC-NOS	1.409 (1.164-1.705)	<0.001
SCLC	1.280 (1.094-1.498)	0.002

NSCLC-NOS: Non-small cell lung cancer not otherwise specified; SCLC: small cell lung cancer.

more pack-years and with lower body weight. Similarly, more symptoms were observed in patients with small cell cancer and in higher TNM stages. These results are in agreement with those of the Spanish study published in 2021 (4). In this study among the group of 267 patients, 33% were asymptomatic, had higher TNM stages patients and exhibited more symptoms; hemoptysis occurred in 11.5% patients. The entire surveyed cohort comprised 16% of asymptomatic patients and hemoptysis was observed in 9.7% of all patients.

When analyzing the individual symptoms within the entire cohort, we found that cough occurred significantly more frequently in younger patients with squamous and small cell lung cancer. Similarly, study performed in the United Kingdom demonstrated the link between the squamous (though not small cell) type of lung cancer and cough (5).

More men than women experienced weight loss. The majority of cases were patients with the squamous type of tumor; patients with adenocarcinoma had lost weight significantly less often before the diagnosis of lung cancer. On the contrary, patients with metastases reported weight loss significantly more frequently than those who had no

metastases. The same results (more frequent weight loss in men compared to women, in patients with squamous cell carcinoma and in patients with metastases) have been described in a study from Brazil where a group of 552 patients with stage IV lung cancer was evaluated. They demonstrated a statistically significantly shorter survival of patients suffering anorexia and weight loss compared to patients devoid of these symptoms (6).

More men than women suffered from hemoptysis, which was more common in heavy smokers. Interestingly, we demonstrated a higher incidence of hemoptysis in taller and heavier patients. We were also surprised by the fact that hemoptysis occurred most frequently in patients with middle lobe cancer (14.1%). On the contrary, the fact that hemoptysis was most common in patients with squamous cell carcinoma and that its frequency increased with the size of the tumor confirmed our previous experience and the findings presented in a British study (5).

As far as fevers are concerned, which were reported by 5.6% of all evaluated patients, we were not surprised that they were more common in younger patients. On the other hand, we cannot explain why fevers occurred statistically significantly more often in taller patients. We were also surprised to find out a statistically significantly higher frequency of febrile episodes in patients with involvement of mediastinal lymph nodes (N2). To the best of our knowledge, the scientific literature does not mention any such linkage. The phenomenon could probably be explained by greater pressure on the surrounding bronchi and more frequent pneumonia due to the stenosis.

The survival analysis showed that the symptoms have an unexpected high predictive capacity. We demonstrated that the groups of alive versus deceased patients differed according to the number of symptoms, and that the three groups of patients classified according to the occurrence of symptoms (asymptomatic, 1-2 symptoms, 3 more symptoms) differed significantly in the time of survival, even after adjustment for age. The same conclusions were drawn by Athey *et al.* (5), who demonstrated a statistically significant association between the survival and symptoms of a group of 3,800 lung cancer patients observed between 1997 and 2011. They recorded the best prognosis in patients with cough, and the worst in patients with neurological symptoms. By analogy, Polanco *et al.* have demonstrated a significantly better prognosis for asymptomatic individuals with lung cancer. In their cohort, asymptomatic patients showed a 3-year survival of 63.6%, whereas 30.3% of symptomatic patients survived for 3 years (4).

On the contrary, the evaluation of 1,546 patients who underwent lung resection for lung cancer at a thoracic surgery center in the north-west England was concluded without evidence of a better prognosis for asymptomatic *vs.* symptomatic lung cancer patients ( $p=0.489$ ) (7).

The shorter follow-up of patients (the first subjects were included on June 1, 2018) and the subsequent lower maturity of data for OS evaluation are the limitations of this study. In conclusion, our study points to the negative predictive significance of symptoms in patients with lung cancer, even after adjustment for age, TNM, PS and morphological type of the carcinoma. This association was further accentuated by the number of symptoms reported by the patients.

### Conflicts of Interest

The Authors declare no conflicts of interest in relation to this article.

### Authors' Contributions

MM and M Svaton conceived the presented idea. MM, ZCH, LFCM, OV, JS, OF, AM, LH, ZG, MH, MJ, JK, DK, MB, JA, M Svovoda and M Svaton conceived and planned the experiments and collected the data. MM, M Svaton and M Svoboda analyzed the data. MM wrote the article with support from M Svaton. JA helped supervise the project. All Authors read and approved the final manuscript.

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