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Decade of lung cancer in Serbia: tobacco abuse and gender differences

J. DJEKIC MALBASA[1,2], T. KOVACEVIC[2,3], B. ZARIC[2,4], T. DUGANDZIJA[1,5], B. NIKOLIN[4,5], D. RADOVANOVIC[5,6], M. PAUT KUSTURICA[7]

[1]Department of Epidemiology, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[2]Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia
[3]Department of Geriatrics, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[4]Department of Internal Medicine, University of Novi Sad, Novi Sad, Serbia
[5]Oncology Institute of Vojvodina, Sremska Kamenica, Serbia
[6]Department of Anesthesiology and Perioperative Medicine, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[7]Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

Abstract. – OBJECTIVE: Lung cancer (LC) is one of the most frequently diagnosed cancers and the leading cause of cancer mortality worldwide. The aim of this study was to get a comprehensive insight into the epidemiology of LC among patients in Vojvodina, the Northern Serbian region, during the ten-year period.

PATIENTS AND METHODS: This retrospective study was performed using LC hospital registry data of the Institute for Pulmonary Diseases of Vojvodina (IPBV) from 2011 to 2020. All patients reported in the registry with a place of residence in Vojvodina were included in this study. The data used in this research were: date of diagnosis, gender, age at diagnosis, place of residence, smoking habits at diagnosis, the intensity of smoking (pack/years), ECOG performance (0-5), histological cancer type, TNM classification and disease stage.

RESULTS: A total of 12,055 LC patients were included, 69.6% of whom were male. The percentage of female LC patients significantly increased, from 26.9% in 2011 to 35.9% in 2020 ($p<0.001$). Non-small cell lung cancer (NSCLC) was diagnosed in 80.8% of patients, while 15.4% of patients had small cell lung cancer (SCLC). The most common histological type was adenocarcinoma (41.9%), followed by squamous cell carcinoma (30.0%) and SCLC (15.4%).

CONCLUSIONS: The number of diagnosed LC patients in the Northern Serbian region increased over the past decade and is significantly higher in females. There was a strong correlation between smoking habits and LC in both genders. Our results also indicate the importance of introducing and promoting LC screening programs for all risk populations, particularly current and ex-smokers of younger age.

Key Words:
Lung cancer, Epidemiology, Serbia, Smoking habits.

Introduction

Lung cancer (LC) is one of the most common cancers and the leading cause of cancer mortality worldwide, especially in men. At the same time, in females, it ranks third for incidence, after breast and colorectal cancer, and second for mortality, after breast cancer[1]. Globally, in 2020 there were an estimated 2.2 million newly diagnosed LC patients and 1.8 million deaths caused by LC. LC incidence and mortality rates are around two times higher among males than females due to the earlier onset of the tobacco consumption epidemic and a higher smoking intensity among males. Also, LC incidence and mortality rates are 3 to 4 times higher in Western than in developing countries; observed trends are a consequence of the tobacco epidemic in these regions[1-3].

Several factors may influence the differences in the gender distribution of LC. It is unknown if the LC risk factors may differ between men and women. There is some evidence that smoking, passive smoking, diet, occupation, indoor exposure, and host factors can protect or facilitate the development of LC[4,5]. Although there is an unclear risk of LC cancer development between males and females, there are differences regarding the distribution of histology types. Thus, squamous cell carcinoma (SCC) and small cell lung carcinoma (SCLC) are more frequent in

Corresponding Author: Milica Paut Kusturica, MD; e-mail: milica.paut-kusturica@mf.uns.ac.rs

males, while adenocarcinoma is more frequent in females. Mentioned differences can potentially be explained by the differences in the consumption of tobacco type between males and females (dark *vs*. blond tobacco consumption has been more frequent in males)[6,7]. Additionally, males are more likely to be diagnosed at a more advanced stage of LC, but the literature that formally compares the stage of diagnosis of LC regarding gender is insufficient[6]. Smoking is the most important cause of LC, counting for 90% in men and 80% in women. Most diagnoses of LC are due to smoking[8], but the strength of association and the corresponding attributable fraction vary greatly by histological type. Thus, SCLC and squamous cell LC are thought to be almost exclusively due to smoking, and other types of LC, like adenocarcinoma, are less dependent on smoking habits[2,9,10].

The smoking epidemic began in the middle of the 20th century in highly developed countries. Consistent application of tobacco control policy and progress in smoking cessation has decreased the incidence and mortality in these regions since the beginning of the 21st century, especially in men. However, in contrast to males, the incidence and mortality of LC among females are still increasing in most European countries, while in the USA is decreasing[2].

During the last decade, a slight decline in tobacco smoking prevalence among the adult Serbian population has been registered (from 33% to 27.1%), mainly due to a decrease in the frequency of smoking among males (from 40.6% to 29.4%). However, the percentage of tobacco abuse is still much higher than the world and the European average (21% and 28%), respectively. In 2019, Serbia was in 5th place among European countries in terms of smoking prevalence, after Greece (42%), Bulgaria (38%), Croatia (36%) and Latvia (32%)[11].

The LC morbidity and mortality rates in Serbia are among the highest in the world. According to the World Health Organization (WHO) estimation for 2020, Serbia ranks second for incidence (50.1/100,000 *vs*. 47.3/ 100,000) and mortality rates (42.4/100,000 *vs*. 40.0/100,000), right after Hungary[2,12]. Compared with Western countries, where a decline in mortality rates has been observed in recent decades, especially for males, mortality rates in Serbia have been continuously rising in both genders, especially female[13].

The Autonomous Province of Vojvodina (Vojvodina), the Northern province of Serbia, with a population of approximately 2 million inhabitants (representing 27% of the total Serbian population) is a multi-ethnic and multi-cultural region. According to the national data, Vojvodina, compared to the rest of Serbia, has the highest incidence (80.8 *vs*. 71.0/100,000) and mortality rates (31.9 *vs*. 27.5/100,000), and the highest prevalence of tobacco consumption compared to the other region of Serbia. Incidence rates in males are around 2.3 times higher than in females. The incidence rates regarding gender are also higher in Vojvodina (144.6/100,000) compared to the rest of Serbia (125.4/100,000) for males, and for females (61.2 *vs*. 52.6/100,000, respectively)[13]. Institute for Pulmonary Diseases of Vojvodina (IPBV) is the only tertiary healthcare institution in Vojvodina intended to diagnose and treat LC patients. The hospital LC registry in the IPBV was established in 2009. Variety in the histological profile of LC in Serbia have been poorly described in the literature. Therefore, our experience and a detailed LC register allowed us to describe and improve our understanding of the epidemiology of LC, including histology, age and gender distribution, stage of the disease, smoking habits, and other patient characteristics in the Northern Serbian region during the ten-year period.

Patients and Methods

This retrospective study was performed using IPBV LC registry data from 1st January 2011 to 31st December 2020. Only patients reported in the LC hospital registry with a place of residence in Vojvodina were included in this study. Patients' data were registered at the time of LC diagnosis. In this research, we used the following variables from the LC registry: date of diagnosis, gender, age at diagnosis, place of residence, smoking habits at diagnosis (current, ex, never smoker), the intensity of smoking (pack/years), the Eastern Cooperative Oncology Group (ECOG) performance status (0-5), histological cancer type, the tumor, node, metastasis (TNM) classification and disease stage (1-4). Different categories of smoking status are defined as: never smoked (smoked less than 100 cigarettes over the lifetime), ex-smoker (quit smoking more than one year before the LC diagnosis), or current smoker (reported smoking habit during the year or more, before the LC diagnosis)[6]. Pack-years (PCKY), or the number of cigarettes a person has smoked throughout their life, was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Personal patient

data were de-identified and encoded during the process of data sampling, and the General Data Protection Regulation (GDPR) protocol was applied[14]. This retrospective study was reviewed and approved by the Institutional Review Board and Institutional Ethical Board of the IPBV (approval number: 1745/1, date: 31/05/2021).

Statistical Analysis

A descriptive statistical analysis was performed. Quantitative variables are presented as mean and standard deviation (SD). We compared patients' characteristics by gender and by smoking habits (current smoker, ex-smoker, and never smoked), across the analysis. The existence of any association by investigated variables was determined using the Chi-square test, Student's *t*-test or the one-way ANOVA. All analyses were performed using the SPSS v. 24.0 computer software program (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p<0.05$.

Results

This study included a total of 12,055 LC patients, where 69.6% of them were male and 30.4% were female. The majority of LC patients lived in the urban areas of Vojvodina at the time of diagnosis (64.6%). The percentage of female LC patients living in urban areas was significantly higher than males (70.9% *vs.* 61.9%, respectively; $p<0.001$). Most LC patients, at the time of diagnosis, were current smokers (61.9%). There were significant differences in the percentage of male and female ex-smokers (30.6% *vs.* 17.8%, respectively; $p<0.001$) and males and females who never smoked (5.1% *vs.* 18.3%, respectively; $p<0.001$) (Table I).

Out of the total observed LC patients included in this study, there were 9,750 (80.8%) patients diagnosed with non-small cell lung cancer (NSCLC) and 1,858 (15.4%) patients with small cell lung cancer (SCLC). The most common

Table I. Demographic and clinical characteristics of lung cancer patients by gender, 2011-2020.

	Total (n)	Male n (%)	Female n (%)	*p*-value*
Characteristics of lung cancer patients	12055 (100.0)	8390 (69.6)	3665 (30.4)	< 0.001
Age (average ± SD)	64 (64.21 ± 8.65)	65 (64.56 ± 8.45)	64 (63.43 ± 9.04)	< 0.001
Settlement area, n (%)				< 0.001
Urban	7792 (64.6)	5194 (61.9)	2598 (70.9)	< 0.001
Suburban or rural	4263 (35.4)	3196 (38.1)	1067 (29.1)	< 0.001
Smoking habits, n (%)				< 0.001
Current smoker	7461 (61.9)	5209 (62.1)	2252 (61.4)	0.4667
Ex-smoker	3224 (26.7)	2570 (30.6)	654 (17.8)	< 0.001
Never smoked	1096 (9.1)	426 (5.1)	670 (18.3)	< 0.001
Unknown smoking status	274 (2.3)	185 (2.2)	89 (2.4)	0.4968
Pack-years (average ± SD)	48.83 ± 28.27	53.37 ± 29.47	36.67 ± 20.26	< 0.001
Current smokers pack-years	50.13 ± 27.48	55.26 ± 28.70	38.28 ± 19.94	< 0.001
Ex-smokers pack-years	45.76 ± 29.82	49.47 ± 30.64	30.88 ± 20.37	< 0.001
Lung cancer type, n (%)				< 0.001
Adenocarcinoma,	5054 (41.9)	3225 (38.4)	1829 (49.9)	< 0.001
Squamous cell carcinoma (SCC)	3612 (30.0)	2916 (34.8)	696 (19.0)	< 0.001
Large cell carcinoma	60 (0.5)	46 (0.5)	14 (0.4)	0.4601
Carcinoid	76 (0.6)	37 (0.4)	39 (1.1)	< 0.001
Neuroendocrine	301 (2.5)	188 (2.2)	113 (3.1)	0.0034
Not otherwise specified (NOS)	620 (5.1)	433 (5.2)	187 (5.1%)	0.8196
Small cell lung cancer (SCLC)	1858 (15.4)	1213 (14.5)	645 (17.6)	< 0.001
Other types	53 (0.4)	36 (0.4)	17 (0.5)	0.444
Not classified	65 (0.5)	48 (0.6)	17 (0.5)	0.5022
No data	356 (3.0)	248 (3.0)	108 (2.9)	0.6671
Lung cancer stage, n (%)				< 0.001
IA	457 (3.8)	264 (3.1)	193 (5.3)	< 0.001
IB	456 (3.8)	294 (3.5)	162 (4.4)	0.0171
II A	406 (3.4)	268 (3.2)	138 (3.8)	0.0937
IIB	580 (4.8)	406 (4.8)	174 (4.7)	0.8127
III A	1978 (16.4)	1410 (16.8)	568 (15.5)	0.0762
IIIB	2732 (22.7)	1922 (22.9)	810 (22.1)	0.3345

p-values are based on the Chi-square test, Student's *t*-test*, as appropriate.

histological type was adenocarcinoma (41.9%), followed by squamous cell carcinoma (SCC) (30.0%) and SCLC (15.4%). In females, compared to males, were observed a significantly higher percentage of adenocarcinoma (49.9% *vs*. 38.4%), SCLC (17.6% *vs*. 14.5%) and carcinoid tumors (1.1% *vs*. 0.4%) ($p<0.001$), while a percentage of SCC was significantly higher in males than in females (34.8% *vs*. 19.0%, respectively; $p<0.001$) (Table I).

The majority of patients were diagnosed in stages IIIB and IV (64.3%). Females were significantly more often diagnosed in stage IA (5.3% *vs*. 3.1%; $p<0.001$) and stage IB (4.4% *vs*. 3.5%; $p=0.02$) compared to males (Table I).

Significant differences in mean pack/years between males and females with LC were observed (53.37 *vs*. 36.67, respectively; $p<0.001$). At the time of LC diagnosis, intensity and duration of smoking were significantly higher among current smokers compared to ex-smokers (50.13 *vs*. 45.76 pack/years, respectively; $p<0.001$). In addition, male patients compared to females had a significantly higher mean pack/years in a group of current smokers (55.26 *vs*. 38.28 pack/years, respectively; $p<0.001$) and in the group of ex-smokers (49.47 *vs*. 30.88 pack/years, respectively; $p<0.001$) (Table I).

The percentage of female LC patients significantly increased from 26.9% (306/1139) in 2011 to 35.9% (379/1056) in 2020 ($\chi^2=71{,}955$, $df=9$, $p<0.001$) (Figure 1). During the study period, the total number of patients with adenocarcinoma, SCC and SCLC decreased in males, while among females increasing trends for adenocarcinoma and SCC were observed. In both genders, the increasing numbers of patients with not otherwise specified (NOS) NSCLC and neuroendocrine carcinoma, were observed per years (Figure 2, Figure 3).

The average age of patients at the time of LC diagnosis was 64 years, with an observed significant difference by gender. Male LC patients were significantly older compared to females (64.56 *vs*. 63.43 years; $p<0.001$) (Table I). In addition, males were significantly older than females regarding adenocarcinoma (64.16 *vs*. 63.18 years; $p<0.001$), and SCC (65.43 *vs*. 64.70 years; $p=0.03$). Patients with squamous cell carcinoma were significantly older than those with adenocarcinoma, SCLC, carcinoid tumor and other types of LC (63.81, 63.12, 58.07, 60.36 *vs*. 65.29 years, respectively; $p<0.001$). Similar age distribution regarding major LC types was observed by gender (Table II).

Statistical significance was observed with respect to smoking habits and LC type: patients with adenocarcinoma smoked less intensive (pack/years) compared to patients with SCC (45.83 *vs*. 52.48 pack/years; $p<0.000$), SCLC (45.83 *vs*. 49.12 pack/years; $p=0.003$) and NOS (45.83 *vs*. 50.50 pack/year; $p=0.02$). A significant difference ($p<0.001$) in the intensity of smoking (pack/years) between males and females was

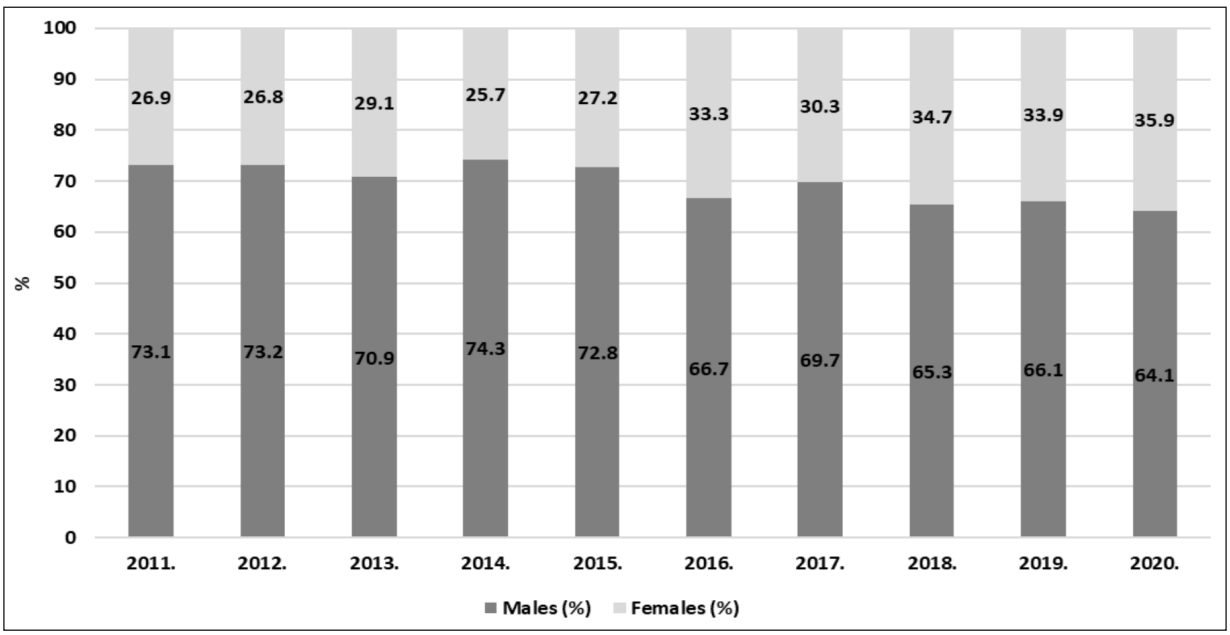

Figure 1. Percentages of lung cancer patients by gender, 2011-2020. SLC-small cell lung carinoma.

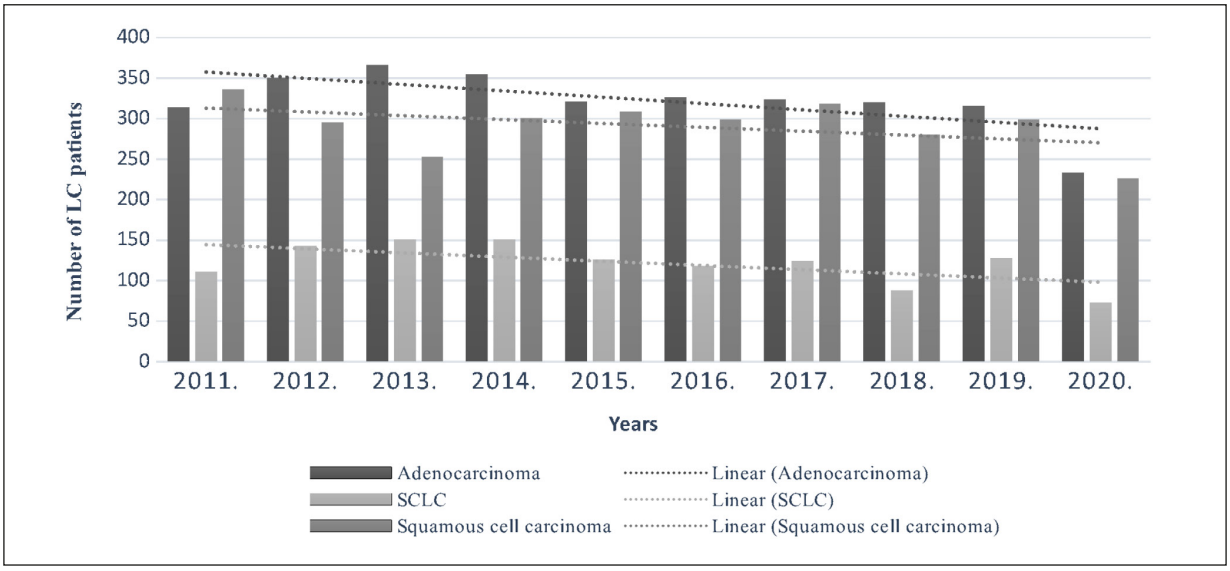

Figure 2. The total number of male lung cancer patients by main histological types, 2011-2020. SCLC-small cell lung carcinoma.

observed among patients with adenocarcinoma (51.93 *vs.* 34.79 pack/years), SCC (55.46 *vs.* 38.81 pack/years), neuroendocrine (57.61 *vs.* 35.19 pack/years), NOS (55.09 *vs.* 37.85 pack/years) and SCLC (53.98 *vs.* 39.32 pack/years) (Table III).

Among current and ex-smokers at the time of LC diagnosis, males were significantly higher percentages (69.8% and 79.7%, retrospectively; $p<0.001$), while in the group of patients who never smoked, most of the patients were females (61.1% *vs.* 38.9%; $p<0.001$) (Table IV).

The mean age of current smokers was significantly lower compared to the mean age of ex-smokers and patients who never smoked (62.50 *vs.* 66.97 and 68.09 years, respectively; $p<0.001$).

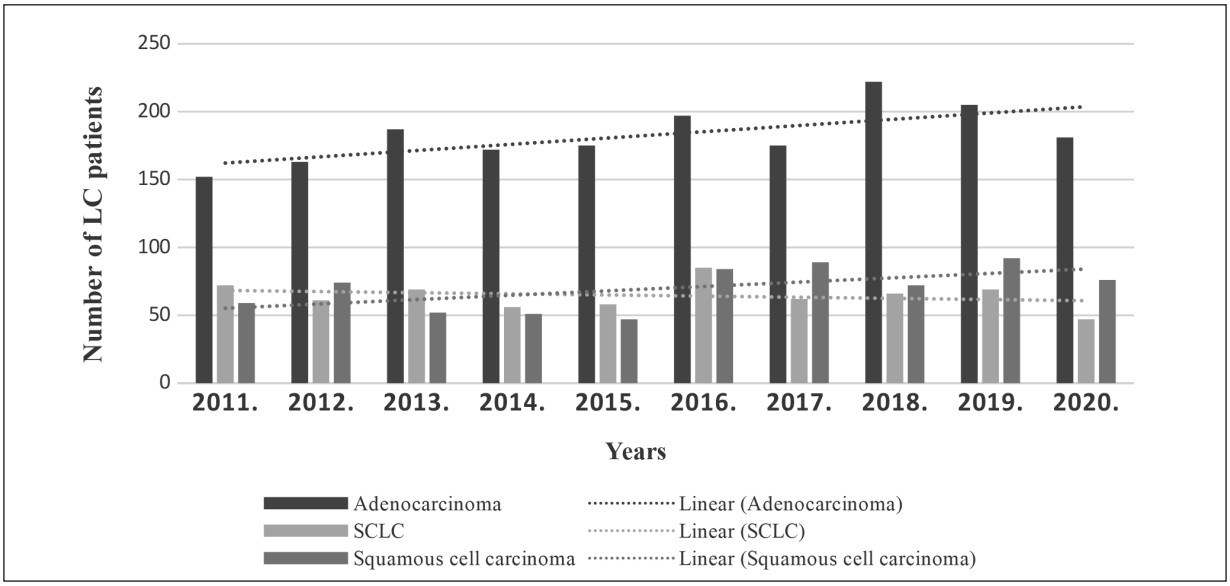

Figure 3. The total number of female lung cancer patients by main histological types, 2011-2020. Abbreviation: SCLC-small cell lung carcinoma.

Table II. Mean age of males and females with lung cancer, according to histological type.

Histological type of lung cancer	Age (mean age ± SD)			
	Male	Female	All	*p*-value
Squamous cell carcinoma (SCC)	65.43 ± 8.07	64.70 ± 8.36	65.29 ± 8.13	**0.033**
Adenocarcinoma	64.16 ± 8.78	63.18 ± 9.50	63.81 ± 9.06	**< 0.001**
Small cell lung cancer (SCLC)	63.24 ± 7.88	62.90 ± 7.67	63.12 ± 7.81	0.393
Neuroendocrine	64.23 ± 8.05	63.42 ± 9.53	63.93 ± 8.63	0.907
Carcinoid	59.59±14.83	56.62 ± 11.17	58.07 ± 13.08	0.458
Large cell carcinoma	63.78 ± 7.00	61.00 ± 8.56	63.13 ± 7.42	0.222
Not otherwise specified (NOS)	65.07 ± 8.20	64.89 ± 8.46	65.02 ± 8.27	0.805
Other types	65.26 ± 8.62	58.88 ± 12.63	60.36 ± 12.08	**0.003**
All	64.56 ± 8.45	63.43 ± 9.04	64.21 ± 8.65	**< 0.001**
p-value	***p* < 0.001****	***p* < 0.001****	***p* < 0.001****	

p-values are based on Student's *t*-test or one-way ANOVA**, as appropriate.

The mean age of females compared to males was significantly lower in the group of current smokers (61.50 *vs.* 62.89 years; $p<0.001$) as well as in a group of ex-smokers (65.02 *vs.* 67.46 years; $p<0.001$), while no difference in age at the time of diagnosis was observed, by gender, among patients who never smoked (68.30 *vs.* 68.09 years; $p=0.382$) (Table IV).

A significantly higher percentage of females compared to male patients with LC lived in urban areas of Vojvodina at the time of diagnosis among current smokers (70.2% *vs.* 60.9%, respectively; $p<0.001$) and ex-smokers (74.5% *vs.* 62.3%, respectively; $p<0.001$). In the group of LC patients who never smoked there were no significant differences regarding gender and settlement area (69.5% *vs.* 68.5%, $p=0.734$) (Table IV). We observed a significant ($p<0.001$) difference in the distribution of LC types by gender and in each of the three groups regarding smoking habits (current, ex, and never smoked) (Table IV).

Regardless of the smoking status, SCC was significantly more common in males than in females; in current smokers (34.9% *vs.* 20.7%, $p<0.001$), ex-smokers (37.9% *vs.* 22.6%, $p<0.001$) and in the group of never smokers (19.0% *vs.* 9.4%, $p<0.001$). Adenocarcinoma was significantly more common in females compared to males, in all three groups stratified by smoking habits; current smokers (44.7% *vs.* 37.1%, $p<0.001$), ex-smokers (49.4% *vs.* 38.1%, $p<0.001$) and never smoked (68.4% *vs.* 54.9%, $p<0.001$). The SCLC was significantly more common among females than in males in current smokers (20.6% *vs.* 16.0%, $p<0.001$) and ex-smokers (16.8% *vs.* 12.1%, $p<0.001$), while no significant difference by gender was found among patients who never smoked (7.9% *vs.* 6.6%, $p=0.423$). The neuroendocrine tumor was significantly common among current smoking females compared to males (3.5% *vs.* 2.5%, $p=0.02$) and ex-smoker females compared to males (3.1% *vs.*

Table III. Mean pack-years by gender and histological lung cancer type.

Histological type of lung cancer	Pack-year (mean ± SD)			
	Male	Female	All	*p*-value
Adenocarcinoma	50.94 ± 28.78	34.79 ± 19.13	45.84 ± 27.17	< 0.001
Squamous cell carcinoma (SCC)	55.46 ± 29.46	38.81 ± 20.97	52.48 ± 28.84	< 0.001
Large cell carcinoma	49.86 ± 37.47	33.50 ± 20.58	46.59 ± 35.21	0.192
Carcinoid	48.50 ± 40.15	29.2262 ± 29.93	38.86 ± 36.31	0.085
Neuroendocrine	55.10 ± 31.01	35.19 ± 17.08	48.07 ± 28.53	< 0.001
Not otherwise specified (NOS)	55.09 ± 29.57	37.85 ± 18.35	50.50 ± 28.08	< 0.001
Small cell lung carcinoma (SCLC)	53.98 ± 28.78	39.32 ± 21.74	49.12 ± 27.17	< 0.001
Other	66.75 ± 59.55	29.27 ± 19.46	54.86 ± 53.10	0.005
p-value	***p* < 0.000****	***p* < 0.000****	***p* < 0.001****	

p-values are based on Student's *t*-test or one-way ANOVA**, as appropriate.

Table IV. Demographic and clinical characteristics of lung cancer patients stratified by tobacco consumption and gender, 2011-2020.

Characteristics	Current smoker			Ex-smoker			Never smoke		
	Male	Female	*p*- value*	Male	Female	*p*- value*	Male	Female	*p*- value*
Lung cancer patients, n (%)	5209 (69.8)	2252 (30.2)	< 0.001	2570 (79.7)	654 (20.3)	< 0.001	426 (38.9)	670 (61.1)	< 0.001
Age (mean ± SD)	63 (62.89 ± 7.98)	62 (61.59 ± 8.22)	< 0.001	68 (67.46 ± 8.02)	65 (65.02 ± 8.51)	< 0.001	68 (67.74 ± 10.84)	68) (68.30 ± 10.00)	0.382
Settlement area, n (%)									
Urban	3174 (60.9)	1582 (70.2)	< 0.001	1602 (62.3)	487 (74.5)	< 0.001	296 (69.5)	459 (68.5)	0.734
Suburban orrural	2035 (39.1)	670 (29.8)		968 (37.7)	167 (25.5)		130 (30.5)	211 (31.5)	
Lung cancer typen (%)			< 0.001			< 0.001			< 0.001
Adenocarcinoma	1931 (37.1)	1006 (44.7)	< 0.001	979 (38.1)	323 (49.4)	< 0.001	234 (54.9)	458 (68.4)	< 0.001
Squamous cell carcinoma (SCC)	1816 (34.9)	467 (20.7)	< 0.001	974 (37.9)	148 (22.6)	< 0.001	81 (19.0)	63 (9.4)	< 0.001
Large cell carcinoma	29 (0.6)	10 (0.4)	0.2791	14 (0.5)	0 (0.0)	0.0700	2 (0.5)	3 (0.4)	0.8072
Carcinoid tumor	10 (0.2)	15 (0.7)	0.001	13 (0.5)	6 (0.9)	0.2296	13 (3.1)	18 (2.7)	0.6985
Neuroendocrine tumor	128 (2.5)	78 (3.5)	0.0163	47 (1.8)	20 (3.1)	0.0368	9 (2.1)	12 (1.8)	0.7241
Not otherwise specified (NOS)	265 (5.1)	125 (5.6)	0.3741	129 (5.0)	24 (3.7)	0.1624	32 (7.5)	35 (5.2)	0.1209
Small cell lung carcinoma (SCLC)	838 (16.1)	465 (20.6)	< 0.001	311 (12.1)	111 (17.0)	0.001	28 (6.6)	53 (7.9)	0.4229
Other	24 (0.5)	8 (0.4)	0.5620	7 (0.3)	6 (0.9)	0.0345	5 (1.2)	3 (0.4)	0.1246
Lung cancer stagen (%)			< 0.001			0.062			0.496
IA	150 (2.9)	115 (5.1)	< 0.001	91 (3.5)	40 (6.1)	0.0025	19 (4.5)	38 (5.7)	0.3848
IB	167 (3.2)	103 (4.6)	0.003	101 (3.9)	29 (4.4)	0.5603	20 (4.7)	29 (4.3)	0.7545
II A	152 (2.9)	92 (4.1)	0.007	96 (3.7)	24 (3.7)	1.000	16 (3.8)	19 (2.8)	0.3586
IIB	251 (4.8)	105 (4.7)	0.8524	130 (5.1)	37 (5.7)	0.5381	21 (4.9)	27 (4.0)	0.4766
III A	856 (16.4)	340 (15.1)	0.1598	478 (18.6)	118 (18.0)	0.7241	59 (13.8)	93 (13.9)	0.9628
IIIB	1208 (23.2)	540 (24.0)	0.4540	596 (23.2)	143 (21.9)	0.4802	81 (19.0)	113 (16.9)	0.3750
IV	2253 (43.3)	880 (39.1)	0.0007	973 (37.9)	247 (37.8)	0.9625	195 (45.8)	338 (50.4)	0.1377

p-values are based on the Chi-square test, Student's *t*-test*, as appropriate.

1.8%, p=0.04), while no significant difference by gender was found among patients who never smoked (1.8% *vs.* 2.1%, p=0.724).

Significant differences in LC stages were observed between males and females among the current smokers. A significantly higher percentage of females compared to males was found in the IA stage (5.1% *vs.* 2.9%, respectively; p<0.001), IB stage (4.6% *vs.* 3.2%, respectively; p=0.003) and IIA stage (4.1% *vs.* 2.9% respectively; p=0.01), while males, compared to females, were significantly more common diagnosed at stage IV (43.3% *vs.* 39.1%, respectively; p=0.001).

Discussion

The predominance of males with LC diagnosis can be found globally[3,6,15-19], with observed differences in percentages of females with LC. Around 30% of patients with confirmed LC in our study cohort were females. In our study, the male to female ratio was 2.3:1, which is in accordance with male to female LC incidence rates registered in Serbia, as well as in the Western countries[1-3,13].

During the observed decade, a significant increase in the number of females with LC was registered. A similar increase has been seen in most Western countries since 2000[1-3,6]. Furthermore, in the observed period, the increasing rates of LC and increasing trends in smoking prevalence in the female population in Serbia have been reported[11,13,20].

There is evidence worldwide that the incidence of LC increases with age, and most LC cases occur at the age of 55-74 years. The median age for LC diagnosis in the USA was 70 years among men and women[2]. In contrast to the USA and some Western countries, where most of the LC cases were registered in the elderly, the median age of our LC patient cohort is lower. The average age of patients at the time of LC diagnosis was 64 years, with an observed significant difference by gender. Women were diagnosed at a younger age than men. Similar age distribution was observed in some other regions[4,6,15-26].

Changes in the epidemiology of LC have been registered worldwide since the 1970s, with an increase in adenocarcinoma and a decrease in squamous cell carcinoma[7,16,17,27]. During the ten-year study period, we observed that the total number of patients with adenocarcinoma, SCC and SCLC decreased in males, while we observed linear trends among females for adenocarcinoma and SCC increase. The increase in adenocarcinoma among smokers could be explained by the introduction of cigarette filters, lower tar and nicotine-contain in cigarettes and a higher level of tobacco-specific nitrosamines[16,17,28,29]. Improvements in diagnostic techniques and additional testing before the introduction targeted (EGFR, *ALK, ROS*, and *BRAF* inhibitors) and immune therapies (PD-1, PDL-1, and CTLA-4 inhibitors) could have influenced the higher incidence of adenocarcinoma. In addition, other factors that could modestly contribute to adenocarcinoma rates in both sexes could be related to air pollution, specifically nitrogen oxides[28].

Concerning histology, in our LC cohort, we found a predominance of adenocarcinoma (40.8%), followed by SCC (29.5%) and SCLC (15.4%). Our results refer to a relationship between LC histology type and gender: SCC is more prevailed in males, while adenocarcinoma in females. Similar findings were prior reported[7,30].

Smoking prevalence among adults in Europe is the highest worldwide, with almost one-third of the population with smoking habits[31]. Although, wide variations between European countries, ranging from 7.2% in Sweden to 36.6% in Greece, were observed[32]. Higher smoking prevalence (over 30%) was observed in central and eastern European countries. The highest smoking prevalence among the female population was registered in Montenegro (>40%), Serbia, and Greece (30-40%). According to WHO's estimation for 2025, the gap between male and female tobacco-smoking prevalence in Serbia will be narrowed and changed due to the permanent increase of smoking prevalence in the female population over the past years[33]. Our results are in line with previous findings as well as with the results of a population survey of smoking prevalence in Serbia, where a decrease in smoking prevalence has been seen in the male but not in the female population[11,20].

Among the observed study population, almost 90% of LC patients were current or ex-smokers at the time of diagnosis, while only 9% of LC patients had never smoked. The predominance of females among never smokers in the LC population has previously been reported[7,6,19] and our study confirmed these findings. In our LC cohort of females, never smoker females with LC were more common, compared to males (18.3% *vs.* 5.1%). On the other hand, a significantly higher percentage of males than females were ex-smokers (30.6% *vs.* 17.8%).

There are some gender-specific differences regarding reasons for starting and maintaining smoking behavior[7,34]. Several scholars[35] observe lower smoking cessation rates among women, although some did not find differences. Anxiety, depression, and high-stress levels, both professional and at home (childcare) are likely causal factors[7]. Because more women are financially independent over the past decades, tobacco companies have intensified targeted advertising and created exclusive cigarette packaging for women. According to the results of the research found in the literature, fear of weight gain discourages women from smoking cessation, and this fear is not considered as important to men[36]. In the USA, tobacco smoking is associated with lower socioeconomic status and racial and gender-identity minorities[2]. Similar findings were reported from the European region. Smoking prevalence was higher among people with lower educational levels and socially disadvantaged groups[33]. Also, a lower smoking prevalence and higher quitting rates were observed among those in higher socioeconomic groups[32]. Similar findings were reported by Goodarzi et al[37], where the declining trend in cigarette consumption was registered in the countries with a high human development index, while its consumption has been increasing in many middle and lower-income countries, such as Serbia. Due to insufficient data, the socioeconomic status of our LC population was not observed in this research.

There is an evidenced correlation pattern between age and LC diagnosis, and our findings align with prior reports[6,36]. We observed that the LC diagnosis at a younger age was followed by higher tobacco consumption. Current smokers, in both genders, were significantly younger than ex-smokers and never smokers at the time of LC diagnosis. At the same time, the PCKY was significantly higher among current smokers than among ex-smokers. We observed a significant age difference among patients with different LC histology, as found in other studies[6]. Our results show that females with adenocarcinoma were younger than females with SCLC or squamous cell carcinoma. The NSCLC is being recognized as a heterogeneous disease in which gender plays a critical and more important role in pathogenesis, diagnosis and treatment than previously appreciated. The complex interactions between biological factors, hormonal differences, environmental and occupational exposures, are just starting to be identified[7,38]. It has been reported that squamous cell lung carcinoma and SCLC are more strongly associated with the smoking habit when compared to adenocarcinoma[28].

Starting smoking at a younger age is also associated with heavy smoking during the lifetime, lower cessation rates, and higher tobacco addiction in adulthood[3,10]. Similarly to prior reports[10], in our LC population, patients with squamous cell lung carcinoma and SCLC have smoked more intensively than patients with adenocarcinoma (52.48, 49.12 *vs.* 45.84 pack-years, respectively). The same intensity of smoking by main LC histological types has been seen in females and in males. However, SCLC was more common among current or ex-smoking males, while the neuroendocrine tumor was more present among the current or ex-smoking female population. These results are similar to other studies[3,6,29].

Furthermore, we observed that adenocarcinoma is the most prevalent histological type diagnosed in never smokers, with higher proportions occurring in the female population. A similar finding was previously reported in studies worldwide[3,6,29]. Also, our results indicate that current females smokers and ex-smokers more often live in urban settings than those never smoker.

Most LC patients are diagnosed with metastatic (stage IV) disease when 5-year survival rates are much lower compared to patients with localized (stage I-II) and regional (stage III) disease at diagnosis[2,39,40].

These findings were also confirmed in our study. More than 40% of LC patients included in our research were diagnosed in stage IV. Contrary to some other findings where LC in the advanced stage at the time of diagnosis was more common in the male population[12], we did not observe significant differences between gender (41.9% of males and 41.0% of females). In addition, the most frequent histological cancer type in our study (adenocarcinoma) was most often diagnosed in stage IV in both genders, while SCC, SCLC, neuroendocrine tumors, and other NSCLC, in both genders, were most commonly diagnosed in stage III. Carcinoid tumor, observed separately, was most commonly diagnosed in stage I of the disease, in both genders. A similar distribution of LC types by gender and stages at diagnosis was reported among Caucasians in USA[41].

Women are likely to be diagnosed with LC at an earlier stage than men[5,27]. In addition, we observed differences by gender and stages of LC among current smokers. Active smoking females

with LC were significantly more commonly detected in the early stages of disease (I and II), in contrast to males, who were more often diagnosed in stage IV of the disease. Observed results can explain better survival in females in our LC population[42].

Limitations

Despite the fact that this was the first long-term research of LC disparities between gender and observed population was more than 12,000 patients, this study has some limitations. First, when talking about smoking habits, there are missing data about the type of cigarettes, as well as, on the patient's socioeconomic status and occupation (working place). Due to past historical events, an unknown number of patients included in this study did not spend their whole life in the observed region, and therefore it was not possible to take into account other LC risk factors. In general, the results of our research represent evidence-based findings and the first insight into epidemiological changes in LC in the last decade. IPBV's LC registry gathered data on about one-third of diagnosed LC patients in Serbia and it could be a starting point for further proposals and changes toward national screening, treatment, and follow-up protocols not only for Serbia but for the whole Balkan region.

Conclusions

The number of diagnosed LC patients in the Northern Serbian region has increased over the past decade, and the observed increase is significantly higher in the female gender. There is a strong correlation between smoking habits and LC in both genders. The LC among the current smoking population is diagnosed at a younger age than among ex- and never-smokers. Female smokers (current and ex) develop LC at a younger age than male smokers (current and ex), although their PCKY is lower than males. Current smoking females were more commonly diagnosed at the early stages of the disease (I and II stages) than males. The narrowed gap between male and female tobacco-smoking prevalence in Serbia is a raising alarm, shown in this research. Effective tobacco control measures and innovative smoking cessation programs for both genders, especially in the female population, are necessary to reduce the high prevalence of smoking in our country. Our results also indicate the importance of introducing and promoting a more active LC screening program for all high-risk populations, particularly current and ex-smokers of younger age.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Jelena Djekic Malbasa: conception and design of the study; Jelena Djekic Malbasa: analysis and interpretation of data; Jelena Djekic Malbasa, Tomi Kovacevic, Bojan Zaric, Tihomir Dugandzija, Borislava Nikolin, Dragana Radovanovic, Milica Paut Kusturica: drafting the article and making critical revisions related to the relevant intellectual content of the manuscript; Jelena Djekic Malbasa: supervision; All authors: final approval of the version of the article to be published.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

Our study was approved by the Institutional Review Board and Institutional Ethical Board of the IIPBV (approval number: 1745/1, date: 31/05/2021).

Informed Consent

This retrospective observational study analyzed depersonalized patient data from the IPBV lung cancer hospital registry. Since the patient informative consent for the recording and the use of data from the lung cancer hospital registry is not a standard part of the IPBV protocol, and as a significant part of the patients included in this study died at the time of data analysis, it was not possible to obtain informed consent.

ORCID ID

Jelena Djekic Malbasa: 0000-0003-4936-2670; Tomi Kovacevic: 0000-0002-2903-5261; Bojan Zaric: 0000-0003-3215-8390; Tihomir Dugandzija: 0000-0001-6279-0413; Borislava Nikolin: 0000-0002-8682-6457; Dragana Radovanović: 0000-0002-5071-7929; Milica Paut Kusturica: 0000-0003-0972-5115.

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