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THE IMPACT OF THE COVID-19 PANDEMIC ON THE LUNG CANCER DIAGNOSIS

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Abstract

Aim: Hospital admissions have been affected by lockdowns during the COVID-19 pandemic. The purpose of this study is to investigate the impact of the COVID-19 pandemic on the lung cancer diagnosis process.

Methods: Patients who attended our clinic after the first official case of COVID-19 in Turkey were diagnosed with new lung cancer via bronchoscopy and/or endobronchial ultrasound and were diagnosed during the fifteen months preceding the COVID-19 pandemic were analyzed retrospectively.

Results: A total of 336 lung cancer patients with a mean age of 64.4±8.9 years, 89.6% male, 197 pre-pandemic, and 139 during the pandemic were included in the study. In this study, 17.6% of the patients applied to the hospital during the lockdown. During the pandemic, the median age of patients was younger, the smoking rate was higher, the rate of admissions with cough was lower (p=0.010), the hemoptysis rate was higher (p=0.012), T stage (p=0.008) increased, and N stage (p=0.001) decreased in newly diagnosed lung cancer patients. There was no significant difference in lung cancer staging between the groups in lockdown. There was no significant difference in metastatic rates between the pandemic and pre-pandemic groups. During the pandemic, the rate of comorbidities decreased in lung cancer patients. The rate of cancer surgery did not change, but the rate of chemotherapy decreased during the pandemic.

Conclusions: The number of newly diagnosed lung cancer cases decreased, and stages changed during the pandemic. Lung cancer diagnosis delays and disease burden are expected to rise in the future.

Keywords: *COVID-19, Lung cancer, lung cancer staging, hospital administration, pandemic*

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Introduction

The first official COVID-19 case was reported in Turkey on March 11, 2020, and the World Health Organization (WHO) declared a COVID-19 pandemic on the same day[1]. After all private and public hospitals in Turkey were declared pandemic hospitals, most of

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the elective tests and surgeries were postponed. A part of health care services in all hospitals is reserved for the pandemic in Turkey. According to WHO data on December 16, 2022, there was 17,004,677 Polymerase chain reaction (PCR) positive COVID-19 cases and 101,419 deaths in Turkey[2].

According to WHO 2021 data, lung cancer is cancer with the highest mortality reported in the world[3]. Symptoms such as cough, dyspnea, and chest pain, which are among the symptoms of lung cancer, are also seen in COVID-19 infections. Imaging methods performed with these complaints may be advantageous for the early diagnosis of lung cancer. However, those who do not have respiratory complaints in the pandemic may not apply to the hospital or may be delayed due to the risk of virus transmission. During the pandemic, worldwide lockdowns, and limitations, as well as in Turkey, may have influenced the behavior of hospital admission rates. For procedures with a high risk of virus transmission, such as bronchoscopy, physicians have moved to preventative measures such as PCR testing and high personal protection equipment during the pandemic. Procedures that provide a high risk of aerosol virus transmission, such as bronchoscopy, were postponed for patients who tested positive for COVID-19 PCR. In the early stages of lung cancer, surgical resection is a possibility, but advanced stages require combinations of chemotherapy and radiotherapy. Mortality and morbidity rise as the stage of lung cancer progresses[4]. Therefore, early diagnosis is an advantage in lung cancer.

This study aims to investigate the impact of the COVID-19 pandemic on the diagnosis and staging process of lung cancer.

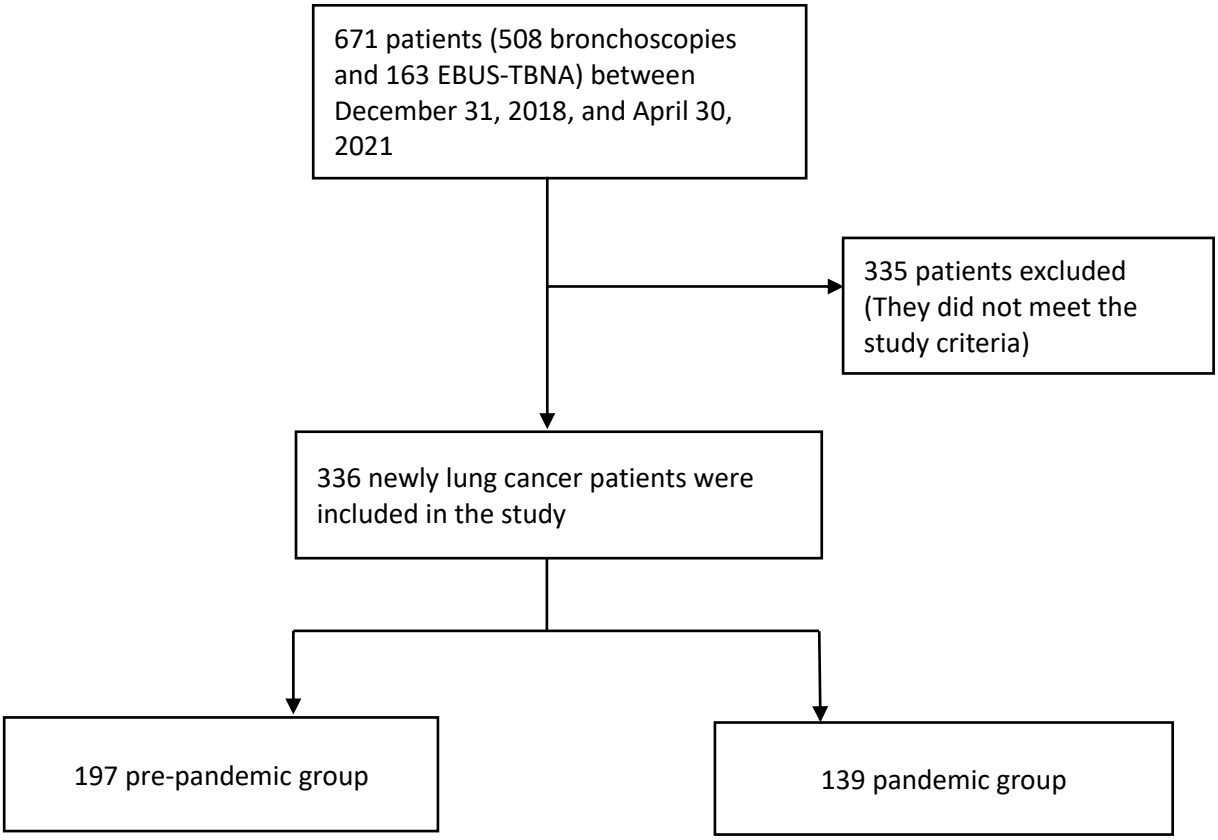

Figure 1. Flow chart for inclusion criteria

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Materials and Methods

Study design and participants

Patients who applied to X University Chest Diseases Clinic between December 31, 2018, and April 30, 2021, and had a bronchoscopy and/or endobronchial ultrasound (EBUS) were included in this single-center, cross-sectional retrospective analysis. The date of the invasive bronchial biopsy and/or lymph node transbronchial needle aspiration (TBNA) procedure was used to distinguish between the pandemic period. The pandemic period was defined as patients treated on or after March 11, 2020.
Inclusion criteria were as follows: age ≥18; pathologically confirmed diagnosis, including non-small cell lung cancer and small cell lung cancer; evaluable lesions in the lungs. Exclusion criteria were as follows: patients previously diagnosed with other tumors such as pulmonary metastatic disease, non-lung cancer, the presence of lymphoma, or other mediastinal tumors; and patients without a pathological diagnosis.

Data collection

The study included 671 participants who had 508 bronchoscopies and 163 EBUS-TBNA between December 31, 2018, and April 30, 2021. Because they did not match the research criteria, 335 patients were excluded. Pre-pandemic 197 and pandemic 139 newly diagnosed lung cancer patients were included in the study (Figure 1). The staging of patients diagnosed with lung cancer at admission was made according to the 8th International Lung Cancer Staging Scale[5]. The patients' age, gender, smoking, stage (TNM), anatomical location of the tumor, pathological diagnosis, comorbidities, surgical treatment, chemotherapeutic treatment, admission complaints, and duration of complaints were all retrospectively analyzed. The overall and local lockdown dates and times were taken from the Republic of Turkey's Ministry of Health statements during the pandemic period. According to the timeline, patients presenting with lockdown restrictions were identified retrospectively[1].

Ethical approval

The STROBE standards for reporting observational studies were followed. This study was approved by the X University Medical Ethics Committee and (No: S-2021-249) Scientific Research Ethics Committee of the Turkish Ministry of Health.

Statistical Analysis

The conformity of the data to the normal distribution was tested with the Shapiro Wilk test. The Mann-Whitney U test was used to compare the non-normally distributed variables in two independent groups. Chi-square and Bonferroni multiple comparison tests were used to test the relationships between categorical variables. SPSS 24.0 software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp.) was used for statistical analyses.

Results

Patient characteristics

The study included 336 newly diagnosed lung cancer patients. In the study, 197 pre-pandemic and 139 pandemic patients were analyzed retrospectively. The mean age of all participants was 64.4 ± 8.9 years, and 89.6% of them were male. In the study, 89.8% of all patients were smokers and had a mean smoked of 44.8 ± 29.6 packs/year. Cough was the most common complaint in newly diagnosed lung cancer patients, and hoarseness was the least. The most common histopathological diagnosis was squamous cell carcinoma (38.7%), and the second most common was adenocarcinoma (32.4%). Anatomically, tumors were most frequently detected in the upper lobe of the right lung (25.5%) and least in the middle lobe of the right lung (5.1%). The most common comorbidity is chronic obstructive pulmonary disease (COPD) (31.5%).

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Table 1. Demographic and clinical characteristics.

Variables		n	Mean ± SD	Median (Min-Max)
Age		336	64.46 ± 8.94	65 (59 -71)
Smoking (packet/ year)		325	44.84 ± 29.69	40 (30-55)
Cough (day)		236	92.89 ± 160.81	30 (30-90)
Dyspnea (day)		188	113.77 ± 183.16	30 (30-90)
Hemoptysis (day)		59	50.76 ± 79.63	30 (10-60)
Chest pain (day)		60	62.02 ± 114.01	30 (30-45)
Sputum (day)		146	83.18 ± 128.16	30 (30-75)
Weight loss (day)		105	82.52 ± 97.9	60 (30-90)
Hoarseness (day)		12	105.58 ± 198.19	37.50 (1-720)
			n	***%***
Sex	Men		301	89.6
	Women		35	10.4
Smoking	Non-smoker		33	10.2
	Smoker		292	89.8
COVID-19 Pandemic	Pre-pandemic		197	58.6
	Pandemic		139	41.4
Lock-down period			59	17.6
Histopathological diagnosis	Adenocarcinoma		109	32.4
	Squamous Cell Ca		130	38.7
	Small Cell Ca		72	21.4
	Large Cell Carcinoma		9	2.7
	NSCLC		12	3.6
	Carcinoid		2	0.6
	Intraepithelial Carcinoma		2	0.6
COVID-19 PCR positive			9	2.7
Asthma			13	3.9
COPD			106	31.5
Hypertension			69	20.5
Diabetes mellitus			59	17.6
Chronic renal failure			4	1.2
Heart failure			43	12.8
Interstitial lung disease			6	1.8
Cancer surgery			67	19.9

COPD, chronic obstructive pulmonary disease.

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The rate of COVID-19 PCR positivity before bronchoscopy/EBUS-TBNA in pandemic patients was 6.4% (Table 1).

Pandemic analyzes.

In comparisons between the pandemic and pre-pandemic periods, patients admitted during the pandemic were statistically younger (p=0.012) and smoked more cigarettes (packs/per year) (p=0.011). In terms of hospital admission complaints, admissions for cough were statistically less common (p=0.010) during the pandemic period, but admissions for hemoptysis were more frequent (p=0.012). When the duration of symptoms until hospital admission was compared, there was no statistically significant difference between the durations of other complaints, except that the duration of expectoration was longer (median=60 days) during the pandemic period (p=0.044). Comorbidities of COPD (p=0.001) and heart failure (p=0.003) during the pandemic period were significantly less. There was a non-significant increase in patients' diabetes comorbidity during the pandemic (p=0.051). All comorbidity rates, except diabetes, of patients admitted to the hospital during the pandemic were reduced, and patients with chronic renal failure and interstitial lung disease did not apply (Table 2).

T stage (p=0.008) increased and N stage (p=0.001) statistically decreased in patients diagnosed with newly lung cancer during the pandemic period. When analyzed with Bonferroni correction; In T staging, the T4 ratio was increased compared to T1 and T2 in the pandemic (p=0.005). In lymph node staging, the N0 rate increased in the pandemic (p=0.001), but the N2 ratio in the pre-pandemic was statistically significantly higher (p=0.001). There was a statistically insignificant increase in the N3 rate in the pandemic. Although there was no statistically significant difference in metastatic rates between pandemic and pre-pandemic, the pandemic metastasis rate was greater (p=0.208). The rate of surgical and radiotherapy treatment of diagnosed lung cancer patients did not differ statistically during the pandemic period. However, the rate of patients receiving chemotherapy was less in the pandemic (p=0.003) (Table 2).

Table 2. Pandemic and pre-pandemic demographics, clinical and stage comparisons.

Variables			Pre-pandemic (n = 197)	Pandemic (n = 139)	P value
Sex	Male		173 (87.8%)	128(92.1%)	0.207
	Female		24 (12.2%)	11(7.9%)	
	Age (n=336)	Median (IQR)	66 (60-71)	64 (57-69)	0.012*
Smoking	Smoker		171 (89.1%)	121 (91%)	0,574
	None-smoker		21 (10.9 %)	12 (9 %)	
Smoking per pack (n=325)		Median (IQR)	40 (30-50)	45 (35-60)	0.011*
Cough			149 (75.6%)	87 (62.6%)	0.010*
Cough (day) (n=236)		Median (IQR)	30 (30-60)	30 (30-90)	0.308
Dyspnea			108 (54.8%)	80 (57.6%)	0.619
Dyspnea (day) (n=188)		Median (IQR)	30 (30-90)	30 (30 -105)	0.373
Hemoptysis			26 (13.2%)	33 (23.7%)	0.012*
Hemoptysis (day) (n=59)		Median (IQR)	30 (10-30)	30 (15-60)	0.592

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Variables		Pre-pandemic (n = 197)	Pandemic (n = 139)	P value
Chest pain		36 (18.3%)	24 (17.3%)	0.812
Chest pain (day) (n=60)	Median (IQR)	30 (30-30)	30 (27.5-67.5)	0.258
Sputum		90 (45.7%)	56 (40.3%)	0.326
Sputum (day) (n=146)	Median (IQR)	30 (30-60)	60 (30-105)	0.044*
Weight loss		63 (32%)	42 (30.2%)	0.731
Weight loss (day) (n=105)	Median (IQR)	45 (30-60)	60 (30-120)	0.135
Hoarseness		7 (3.6%)	5 (3.6%)	0.983
Hoarseness (n=12)	Median (IQR)	45 (30-90)	30 (20-90)	0.755
T		n (%)	n (%)	
· 1		23 (11.7)	7 (5.1)	
· 2		62 (31.5)	28 (20.3)	0.008*
· 3		24 (12.2)	20 (14.5)	
· 4		88 (44.7)	83 (60.1)	
N		n (%)	n (%)	
· 0		21 (10.7)	38 (28.1)	
· 1		25 (12.7)	11 (8.1)	0.001*
· 2		99 (50.3)	43 (31.9)	
· 3		52 (26.4)	43 (31.9)	
· Metastasis		90 (45.9)	72 (52.9)	0.208
Lung Cancer Stage		n (%)	n (%)	
· 1A		5 (2.6)	2 (1.5)	
· 2A		2 (1)	6 (4.4)	
· 2B		12 (6.1)	7 (5.1)	
· 3A		40 (20.4)	25 (18.4)	0.182
· 3B		36 (18.4)	16 (11.8)	
· 3C		12 (6.1)	8 (5.9)	
· 4A		13 (6.6)	17 (12.5)	
· 4B		76 (38.8)	55 (40.4)	
		n (%)	n (%)	
Asthma		8 (4.1)	5 (3.6)	0.828
COPD		80 (40.6)	26 (18.7)	0.001*
Hypertension		46 (23.4)	23 (16.5)	0.128
Diabetes mellitus		28 (14.2)	31 (22.5)	0.051
Chronic renal failure		4 (2)	0 (0)	0.091
Heart Failure		34 (17.3)	9 (6.5)	0.003*
Interstitial lung disease		6 (3)	0 (0)	0.038*
Cancer surgery		43 (21.8)	24 (17.3)	0.303
Chemotherapy		148 (77.9)	85 (63)	0.003*
Radiotherapy		72 (38.3)	55 (40.4)	0.697

Abb: SD, std. deviation; IQR, interquartile range; *Significant p value < 0.05; Mann Whitney u test for numerical, Chi-square test for categorical data; COPD, chronic obstructive pulmonary disease.

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Table 3. Symptom and stage comparisons of the lockdown period in the pandemic.

	Lock-down				
	Yes		No		
N = 59	*n*	%	*n*	%	*P value*
Cough	43	72.9	43	54.4	0.027*
Dyspnea	34	57.6	45	57.0	0.938
Hemoptysis	18	30.5	15	19.0	0.116
Chest pain	14	23.7	10	12.7	0.090
Sputum	29	49.2	27	34.2	0.076
Weight loss	18	30.5	24	30.4	0.987
Hoarseness	2	3.4	3	3.8	0.899
T					
· 1	2	3.4	5	6.3	0.645
· 2	14	24.1	14	17.7	
· 3	7	12.1	13	16.5	
· 4	35	60.3	47	59.5	
N					
· 0	17	30.9	21	26.6	0.552
· 1	3	5.5	8	10.1	
· 2	20	36.4	23	29.1	
· 3	15	27.3	27	34.2	
· Metastasis	33	58.9	39	49.4	0.273
Stage					
· 1A	1	1.8	1	1.3	0.331
· 2A	3	5.4	3	3.8	
· 2B	0	0.0	7	8.9	
· 3A	10	17.9	15	19.0	
· 3B	6	10.7	10	12.7	
· 3C	2	3.6	5	6.3	
· 4A	10	17.9	7	8.9	
· 4B	24	42.9	31	39.2	

* Significant at the 0.05 level; Chi-square test.

Hospital admissions of 17.6% of all patients were in the lockdown period. When patients (42.4%) coinciding with the date of hospital admission closure restrictions in the pandemic are grouped; in the pandemic, there was a statistically higher increase in cough during the closure period (p=0.027) (Figure 2), and an insignificant increase in sputum (p=0.076). The rate of other application complaints was similar. There was no statistically significant difference in lung cancer staging between the groups in lockdown (Table 3).

Discussion

The COVID-19 pandemic has put a serious strain on healthcare systems around the world. Particularly for the first year of the pandemic in Turkey, some of the health units for COVID-19 patients in all hospitals were

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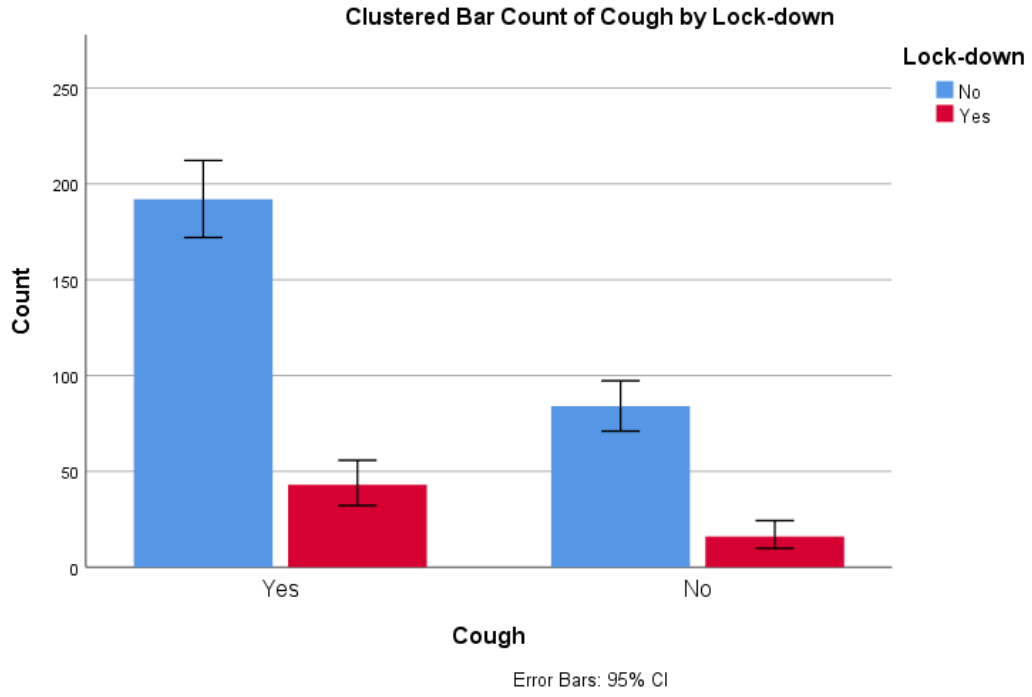

Figure 2. Comparison of cough complaints in the pandemic during the lockdown period (p = 0.027)

allocated to the pandemic. Understandably, various restrictions and lockdown decisions have been made all over the world to reduce virus transmission. In Turkey, curfews have been implemented in addition to the general closure for those over the age of 65 and those with comorbidities[6]. Admission to the hospital was partially difficult in the diagnosis and follow-up of other infections, cancer, cardiovascular diseases, and chronic respiratory diseases other than COVID-19. Fear of the risk of virus transmission may have influenced hospital admissions. Worldwide, non-COVID-19 disease applications and follow-ups have been disrupted. Delays in the treatment and follow-up of lung cancer have been reported during the pandemic period[7]. The pandemic is predicted to result in an increase in cancer-related mortality in the United Kingdom due to delayed diagnosis[8]. In the pandemic, the United States expected excess deaths were shown to increase by 20% in the period March-July 2020[9].Lung cancer is one of the most common cancers with the most reported mortality[3]. Lung cancer diagnosis, treatment, and follow-up should continue in the event of a pandemic.

Bronchoscopy/EBUS procedures were continuing in our clinic during the COVID-19 pandemic. The follow-up and treatment of non-COVID-19 lung diseases continued at our chest diseases clinic. Despite this, fewer patients (N=139) were diagnosed with newly lung cancer during the 15-month period of the pandemic. In other studies, fewer new lung diagnoses were made during the pandemic period and less invasive techniques were used[10,11]. In our study, it was found that the average age of lung cancer during the pandemic period was younger. In a study conducted in China during the pandemic, lung cancer patients during the pandemic were significantly younger[12]. Curfews over the age of 65 and fear of infection may have an impact on hospital admissions. Being over 65 years old has been shown to be an independent risk factor for COVID-19 mortality[13]. Health authorities in Turkey called for people over the age of 65 to stay at home frequently. Curfews for those over the age of 65

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were imposed by the government during the pandemic[1]. Due to the risk of transmission of COVID-19, the application of patients over the age of 65 may be delayed. From another point of view, thorax CT (computed tomography) scans performed with the suspicion of COVID-19 may have offered the possibility of diagnosis at a younger age.

Most of the pulmonary symptoms of lung cancer can also be seen in COVID-19 infection. While COVID-19 can be asymptomatic, it can also cause cough, dyspnea, and chest pain. On the other hand, hemoptysis is not an expected complaint of COVID-19[13]. Patients diagnosed during the pandemic period had fewer cough complaints at admission, but a higher rate of hemoptysis. While cough is a delayed complaint, hemoptysis seems to accelerate hospital admission. Other pulmonary complaints, weight loss, and hoarseness rates of patients diagnosed with lung cancer did not show a significant difference in the pandemic. On the other hand, the duration of complaints was longer for those with sputum during the application complaint period. Sputum production was the most delayed complaint. Cough was significantly more common among the admission complaints of the patients subject to lockdown in the pandemic, and the rate of other complaints was similar. Patients with coughs were admitted to the hospital more during lockdown periods. The periods of curfews were the times when the number of COVID-19 cases and the number of tests increased. Patients with a negative COVID-19 test and cough may have applied to pulmonary medicine clinics. Some of the mildly symptomatic patients with suspected COVID-19 infection were isolated at home. However, some of the patients who are not tested may have non-COVID-19 diseases.

In this study, 89.8% of lung cancer patients were smokers/ex-smoker. Patients diagnosed with lung cancer in the pandemic were more likely to smoke than the pre-pandemic group. A higher percentage of smokers and patients with pulmonary complaints were admitted to our clinic. A cohort of newly diagnosed lung cancer cases was reported to have a six-times higher prevalence of COPD than cancer-free smokers[14]. The prevalence of COPD was 31.5% in the group of patients with a newly lung cancer diagnosis with high smoking. The comorbidity rates of COPD and heart failure during the pandemic period were significantly reduced. Hospital admissions of patients with comorbidities were lower than before the pandemic. In a multi-center study conducted in Turkey, COPD, heart failure, hypertension, and interstitial lung disease comorbidities were found to be associated with COVID-19 mortality[13]. Patients with comorbidities are in the risk group for COVID-19 mortality. All non-COVID-19 hospital admissions may have decreased during the pandemic. There were fewer lung cancer patients diagnosed in our clinic during the pandemic in the same period.

The pandemic had an impact on the lung cancer stage in our study. The most noticeable effect was in the T phase, where the T4 ratio was higher than before the pandemic in lung cancer cases. If the N-stage is low and there is only one N2, there is a chance for surgery in individuals with an enhanced T-stage. However, neoadjuvant therapy may be required in stage III patients before surgical resection[15]. Interestingly, lymph node staging was significantly increased in the N0 direction during the pandemic, so patients might have a chance for surgery even if their T-stage was increased. The pandemic did not change the lung cancer metastasis rates of patients. In similar studies, the pandemic did not cause major stage changes in lung cancer[10–12].

In this study, the rate of lung resection surgery in lung cancer patients did not change during the pandemic. At the same time, the rate of patients receiving chemotherapy decreased in the pandemic, and the rate of radiotherapy was the same. Studies have shown delays in lung cancer surgery during the pandemic[16]. The need for repeated hospital admissions for chemotherapy may have reduced this rate. Being infected or in contact with COVID-19 during the pandemic process may have affected the admission and/or continuity of chemotherapy. Lung cancer surgery and chemotherapy treatments may show

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regional and center-based changes. However, the pandemic may have affected the individual surgical decision of the patients and their treatment requiring other hospital admissions. Newly diagnosed lung cancer patients had reduced mortality rates during the pandemic, although it should be remembered that the time they were diagnosed (from the start of the epidemic to the completion of the study) was shorter.

- **Limitations**

Although the study is large enough to show many effects of the pandemic on the diagnosis and staging of lung cancer, there are some limitations. First of all, the study is not multicenter research. So, the effect on the number of hospital admissions and lung cancer cases in different centers is unknown. Recurrent lung cancer cases were not included in the study, but these cases also had pulmonary symptoms that had just started in the pandemic. As a result, a multicenter study covering new and recurrent lung cancer cases may show different results.

Conclusion

This study showed the impacts of the COVID-19 pandemic on lung cancer symptoms, diagnosis, stage, and treatment. The effects of lung cancer diagnosis and disease burden should be monitored in the coming years. In extraordinary situations affecting health systems such as pandemics, there is a need for regulations that will not disrupt the diagnosis and follow-up of lung cancer. Telemedicine methods can be developed to facilitate access to the hospital for populations at risk during the pandemic.

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Conflict of interest
The authors declare that they have no conflict of interest.

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Ethical approval
This study was approved by the Gaziantep University Medical Ethics Committee and (No: S-2020-249) Scientific Research Ethics Committee of the Turkish Ministry of Health.

Contribution of the authors:
FF and NO designed the study; FF and NO collected the data; FF analyzed the data; FF searched the literature and wrote the manuscript; FF edited and revised the manuscript according to the journal's instructions; FF prepared tables and figures; FF edited and controlled the final version of the manuscript. All the authors approved the final version of the manuscript.
The manuscript has been read and approved by all the authors.

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