The Impact of the COVID-19 Pandemic on the Diagnosis and Treatment Characteristics of Operated Lung Cancer Patients

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ABSTRACT

Objective: To analyse the impact of the COVID-19 pandemic on the diagnostic method, disease stage, treatment modalities, and survival of operated non-small cell lung cancer (NSCLC) patients.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Oncology, Gaziantep University Oncology Hospital, Sahinbey, Turkey, from March 2018 to March 2022**.**

Methodology: Patients who were operated for NSCLC were screened retrospectively. The diagnostic method, demographic and clinical characteristics of patients, COVID-19 infection and survival time were analysed and compared after dividing the patient into prepandemic and pandemic groups according to their chronology of enrollment.

Results: A total of 303 patients were included in the study (prepandemic=163, pandemic=140). The time from the symptom onset to the histological diagnosis was shorter in the pandemic group (p=0.005). T4 tumours were more common in the prepandemic group (p=0.01). Most patients with adenocarcinoma underwent lobectomy, and most patients with pneumonectomy had squamous cell carcinoma (SCC) histology (p=0.001). The indications for chemotherapy and radiotherapy significantly differed between the groups (p=0.005 and p=0.001, respectively). The rate of patients with incidental diagnosis was higher in the pandemic group (p=0.001), often at Stage-1; patients diagnosed with symptoms were often at Stage-3 (p=0.001). Among the incidentally diagnosed group of patients, 34 (72%) had adenocarcinoma; 127 (50%) patients in the group diagnosed with symptoms had SCC subtype (p=0.001).

Conclusion: During the pandemic, proportion of patients diagnosed incidentally increased. These patients were mostly diagnosed with adenocarcinoma subtype and diagnosed at an earlier stage.

Key Words: *Lung cancer, Incidentally, COVID-19 pandemic.*

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INTRODUCTION

A novel coronavirus subtype, called severe acute respiratory syndrome coronavirus-2 (*SARS-CoV-2*), caused Coronavirus disease-2019 (COVID-19).[1] The first case was reported in Wuhan, China at the end of December 2019, and the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020.[2] COVID-19 caused great economic and social losses in many countries, all over the world.[3]

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The first case of COVID-19 was reported in Turkey on March 11, 2020. Transportation restrictions, lockdown, interruption of education and staying-at-home for individuals with chronic diseases were implemented within the first 4 months of the pandemic. In the health care systems, pandemic services, pandemic intensive care units and pandemic hospitals were defined. Vaccination campaign against COVID-19 in Turkey started on January 14, 2021.[4] Turkey ranked 10th in the world in terms of the total number of cases, with 15 million COVID-19 cases and about one hundred thousand deaths in about 2 years.[5]

Given that cancer itself and its treatment cause an immunosuppressive state, COVID-19 has worse prognosis in cancer patients. COVID-19 is considered to be more fatal in haematological cancers, lung cancer and stage-4 cancers.[6] High mortality in lung cancer patients has been related to the fact that *SARS-CoV-2* virus mainly affects the lung, as well as certain

factors such as smoking status, presence of chronic obstructive pulmonary disease, receiving chemotherapy, thoracic radiotherapy or surgical intervention and associated comorbidities.[7]

The impact of the COVID-19 pandemic on the diagnosis and treatment of operated lung cancer patients is unclear. The limited cancer care during the COVID-19 pandemic is considered likely to increase the pathological stage and long-term mortality in lung cancer patients.[8] In Japan, COVID-19 pandemic was associated with having a more advanced disease at the time of initial admission and decrease in surgical treatment rates among lung cancer patients.[9] In South Korea, the admission rates of NSCLC patients with an advanced disease were found to be increased in the pandemic group.[10] Alongside these negative effects, COVID-19 pandemic may also offer an opportunity of early incidental diagnosis and treatment in some patients thanks to the imaging for COVID-19.

The aim of this study was to assess the potential impact of COVID-19 pandemic on the management of newly diagnosed operated NSCLC patients in terms of diagnostic methods, clinicopathological features, and treatments.

METHODOLOGY

This study was conducted at the Oncology Clinic of Gaziantep University, Sahinbey, Turkey. The study was conducted in accordance with the Declaration of Helsinki. The study was reviewed and approved by the University Ethics Committee (Approval no. 2022/143). Patients who were diagnosed in the two years preceding March 11, 2018 to March 11, 2020 comprised the prepandemic group. All patients who were diagnosed between March 11, 2020 and March 11, 2022 comprised the pandemic group. Patients aged >18 years and operated with NSCLC within the study period were included. Patients with known secondary malignancy or those with inoperable metastatic disease or incomplete data were excluded from the study.

Clinical and pathological characteristics of the patients were obtained from hospital medical files or electronic health record systems. The history of lung cancer diagnosis (due to complaints/symptoms or incidentally on radiological imaging) and delay in diagnosis or treatment were investigated. For the delay in diagnosis, the date of radiological diagnosis and the date of histological diagnosis were recorded in both groups. Tumour, node and metastasis (TNM) staging was assessed based on the 8th edition.[11] In patients who were operated without receiving neoadjuvant chemotherapy, tumour diameter (T) and lymph node (N) were determined from the surgical material, while it was determined according to staging at the time of diagnosis in patients who received neoadjuvant therapy. The histological subtypes of the tumour (adenocarcinoma, SCC and other rare subtypes such as large cell cancer, neuroendocrine tumour, neuroendocrine cancer, and pleomorphic carcinoma) were recorded in both groups.

Radiotherapy (RT), chemotherapy (CTx), immunotherapy, and tyrosine kinase inhibitor treatments of the patients were analysed with respect to the potential effect of the COVID-19 pandemic on these treatment modalities. Patients who had positive test of *SARS-CoV-2* RT-PCR for COVID-19 were considered infected with COVID-19.

Overall survival was defined as the time between histological diagnosis and the final follow-up or death, whichever came first. The cause of death (due to cancer, COVID-19 infection or comorbid diseases) was recorded in non-survivors. The date of local recurrence or distant metastasis in the follow-up of the patients was determined as the date of recurrence. Disease-free survival (DFS) was defined as the time between the date of diagnosis and the date of recurrence or the date of the last control or death (whichever occurred first).

The minimum number of subjects required for the statistically significant expectation that the difference between patients diagnosed with COVID-19 in lung cancer and patients diagnosed with physical examination and symptoms was 86 in each group (α=0.05, 1-β=0.90).[12] Relation between categorical variables was tested by Chi-square test. Categorical variables were expressed as numbers (n) and percentages (%). Moreover, independent samples t-test and Mann-Whitney U test were used to compare continuous variables according to the study groups. Continuous variables were expressed as the mean ± standard deviation (SD). Survival analyses such as OS and DFS were performed by Kaplan Meier analysis. Comparisons were made *via* Log-Rank test. Cox regression analysis was used to identify determinants of survival. Statistical analysis was performed using IBM SPSS Statistics for Windows, (IBM Corp., Armonk, NY), version 22.0. The value of $p<0.05$ was accepted for statistical significance.

RESULTS

A total of 303 patients were included in the study (prepandemic=163, pandemic=140). Patients' age at diagnosis, gender, and smoking history were similar between the groups (Table I). Overall, females comprised only 11% of the study population. The diagnosis based on symptoms was the most common type of diagnosis in both groups, whereas the rate of incidental diagnosis was higher in the pandemic group (23 *vs.* 9%, p=0.001). The time (months) between radiological diagnosis and histological diagnosis and between histological diagnosis and surgery were similar between the groups. However, the time between symptom onset and histological diagnosis was significantly shorter in the pandemic group as compared to prepandemic group (median 2(1-2) *vs.* 2(1-3) months), (p=0.005).

The distribution of N stage and TNM stage in the groups were similar. But, T4 tumours were significantly more in the prepandemic group (p=0.01, Table I). The median tumour diameter was 4.5(3.1-7.2) cm in the prepandemic group, 4.2(2.7-6.0)cm in the pandemic group (p=0.188). Distant organ metastasis and recurrence were significantly higher in the prepandemic group (49 *vs.* 25%, p=0.001). Lobectomy was the most commonly performed surgery, and SCC was the most common histological subtype in the groups.

Table I: Baseline characteristics of the patients.

Age (year), Mean±SD		**Prepandemic group (n=163) 64.24 ± 9.73**	**Pandemic group (n=140) 62.49 ± 9.54**	**p-value 0.115***
Gender, n (%)	Female	13 (7.98)	21 (15)	0.053
	Male	150 (92.02)	119 (85)	
Smoking history, n (%)	Current smoker	64 (54.7)	59 (47.58)	0.519
	Former smoker	42 (35.9)	50 (40.32)	
	Non-smoker	11 (9.4)	15 (12.1)	
Type of diagnosis, n (%)	Symptomatic	147 (90.74)	106 (76.81)	0.001
	Incidental	15 (9.26)	32 (23.18)	
Histological subtype, n (%)	Squamous cell cancer	76 (46.63)	60 (42.86)	0.667
	Adenocarcinoma	64 (39.26)	56 (40)	
	Others subtypes	23(14.1)	24(17.1)	
COVID-19 vaccination status, n (%)	No	96 (58.9)	47 (33.57)	<0.001
	Yes	67 (41.1)	93 (66.43)	
COVID-19 infection status, n (%)	No	151 (92.64)	114 (81.43)	0.003
	Yes	12 (7.36)	26 (18.57)	
T-stage	T1	35 (21.47)	41 (29.29)	0.010
	T2	44 (26.99)	37 (26.43)	
	T3	36 (22.09)	42 (30)	
	T4	48 (29.45)	20 (14.29)	
M-stage	M0	147 (90.18)	135 (96.43)	0.033
	M1	16 (9.82)	5 (3.57)	

**Independent t-test was used for age and Chi-square test was used for other parameters. SD: Standard deviation, COVID-19: Coronavirus disease 2019.*

Table II: Treatment indications in both groups and reasons for mortality in non-survivors.

		Prepandemic group n (%)	**Pandemic group n (%)**	**p-value**
Radiotherapy (RT) indications	Not indicated	93 (57.41)	113 (80.71)	0.001
	Definitive CRT	30 (18.5)	11 (7.86)	
	Adjuvant RT	10 (6.17)	4 (2.86)	
	Palliative RT	29 (17.9)	12 (8.57)	
Chemotherapy (CTx) indications	Not indicated	45 (27.61)	50 (35.71)	0.005
	NeoadjuvantCTx	3 (1.84)	6 (4.29)	
	Adjuvant CTx	66 (40.49)	66 (47.14)	
	Palliative CTx	17 (10.43)	5 (3.57)	
	Adjuvant and palliative CTx	32 (19.63)	13 (9.29)	
Surgical procedure	Lobectomy	119 (73.01)	94 (67.1)	0.176
	Pneumonectomy	44 (26.99)	46(32.9)	
Current status of the patient	Active follow-up	66 (40.49)	94 (67.14)	<0.001
	Active treatment	10 (6.13)	12 (8.57)	
	Non-survivor	87 (53.37)	34 (24.29)	
Local recurrence or distant metastasis	No	83 (50.92)	105 (75)	<0.001
	Yes	80 (49.08)	35 (25)	
Cause of death	Due to cancer	66 (75.86)	19 (57.58)	0.049
	Due to comorbidities	21 (24.14)	14 (42.42)	

**The Chi-square test was used. RT: Radiotherapy, CTx: Chemotherapy, CRT: Chemoradiotherapy.*

However, 83% of patients with adenocarcinoma had lobectomy, while 74% of patients with pneumonectomy were SCC patients (p=0.001). Twenty-one patients were oligometastatic; definitive surgery was performed for both primary and metastasis. Among these patients, 16 were in the prepandemic group and 5 were in the pandemic group, and there was a significant difference (p=0.033). Of oligometastatic patients, 18 patients had brain metastectomy and 3 patients had adrenal metastasectomy.

There was a significant difference between the two groups in terms of chemotherapy (CTx) indications and radiotherapy (RT) indications (p=0.005, p=0.001, respectively, Table II). In this cohort, three patients used tyrosine kinase inhibitors and six patients received immunotherapy (mostly nivolumab) in the metastatic period. The rate of vaccination against COVID-19 in the pandemic group was higher than in the prepandemic group (66 *vs*. 41%, p=0.001). The percentage of patients being infected with COVID-19 was 7.3% in the prepandemic group and 18.5% in the pandemic group (p=0.003). One patient in the pandemic group died due to COVID-19.

In the analysis of disease-free survival (DFS) and overall survival (OS), the median survival was not reached in the pandemic group. The median DFS was 23 months (95% CI, 6.3-39.7) in the prepandemic group, and estimated median DFS was 43 months for the overall cohort (p=0.051, Figure 1A). The one- and two-year DFS rates were 66±4% and 50±4%, respectively in the prepandemic group, while one- and two-year DFS rates in the pandemic group were 74±4% and 63±6%, respectively. Metastasis developed in 73(45%) patients in the prepandemic group and 32 (22%) patients in the pandemic group (p=0.001).

The median OS in the prepandemic group was 32 months (95% CI, 20.8-43.2), and estimated median OS was 39 months for the entire cohort (p=0.109, Figure 1B). The one-

and two-year OS rates were 72±3% and 55±4% in the prepandemic group, and 77±4% and 68±5% in the pandemic group, respectively. At the time of analysis, 41% of the patients in the prepandemic group and 67% of the patients in the pandemic group were in remission. In addition, 53% of the patients in the prepandemic group and 24% of the patients in the pandemic group died (p=0.001). The most common cause of death was disease progression in both groups. The percentage of patients who died due to comorbidities was 24% in the prepandemic group and 41% in the pandemic group (p=0.049).

In the subgroup analysis of survival, there was no difference in terms of DFS between patients diagnosed with symptoms and those diagnosed incidentally (p=0.099, Figure 2A). However, the mean OS in patients diagnosed with symptoms was 31±1.5 months, while it was 39±1.9 months in patients diagnosed incidentally (p=0.008, Figure 2B). While 51% of the patients diagnosed incidentally were at Stage-1 and 25% were at Stage-2, 45% of the patients diagnosed with symptoms were diagnosed at Stage-3 and 28% at Stage-2 (p=0.001). In the incidentally- diagnosed group, 34 (72%) patients had adenocarcinoma, and 8 (17%) patients had SCC histology, while in the group diagnosed with symptoms, 127 (50%) had SCC and 84 (33%) had adenocarcinoma subtype (p=0.001).

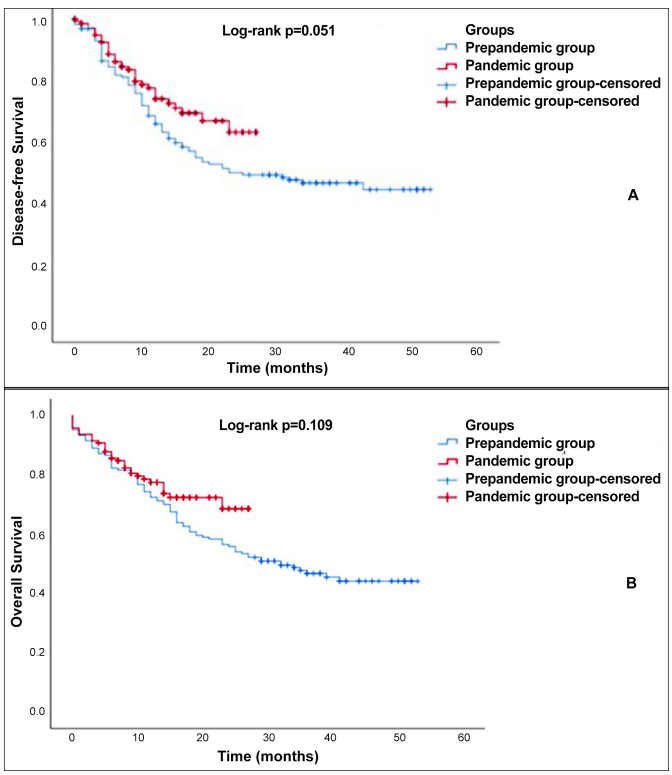

Figure 1: Kaplan-Meier survival analysis prepandemic *vs.* pandemic groups. (A) In the analysis of disease-free survival (DFS), median survival could not be reached due to the short follow-up in the pandemic group. However, the median DFS of all patients was 43 months, while the median DFS was 23 months in the prepandemic group. (B) According to overall survival analysis, the median survival was not reached in the pandemic group, with a median OS of 32 months in the prepandemic group and 39 months in all patients.

In the univariate analysis, age at diagnosis, TNM stage, method of diagnosis, histological subtype, receiving RT and CTx were found to be significant. In multivariate analysis, age at diagnosis, stage of disease and receiving CTx were found to be independent predictors of overall survival (p <0.001, for all three).

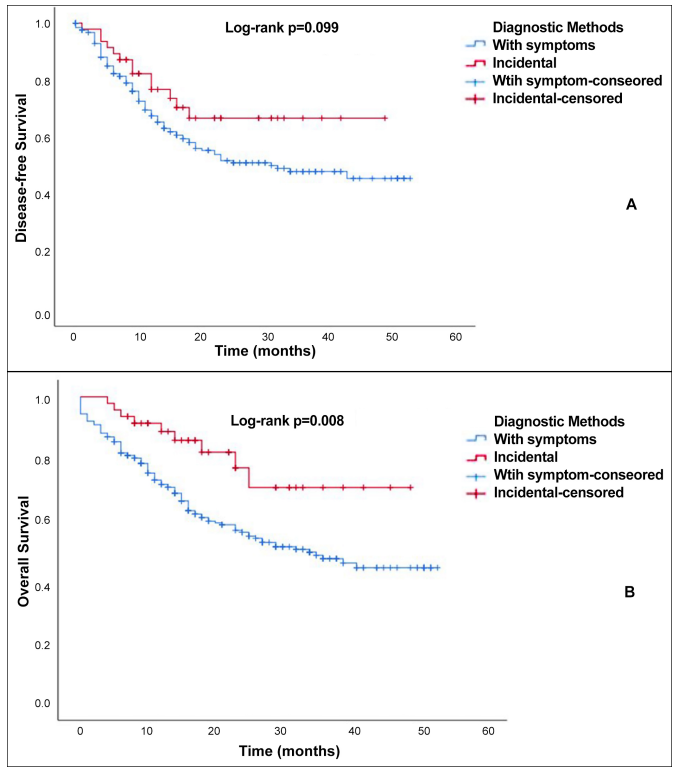

Figure 2: Kaplan-Meier analysis of survival in patients diagnosed incidentally and by symptoms, (A) In the analysis of disease-free survival, the estimated median DFS could not be reached yet in the incidentally--diagnosed group, the median DFS was 32 months in the symptom-diagnosed group, and the median DFS was 43 months in the overall patients. (B) In the overall survival (OS) analysis, the estimated median OS could not be reached yet in the incidentally-diagnosed group, the median OS was 34 months in the symptom-diagnosed group, and the median OS was 39 months in the whole patient group. OS was significantly better in the incidentally-diagnosed group (p=0.008).

DISCUSSION

This study is one of the first studies to examine the effects of the COVID-19 pandemic on operable lung cancer patients. The findings of this study revealed significant differences in the type of diagnosis, tumour stage, treatment modalities, COVID-19 infection and vaccination rates against COVID-19 between prepandemic and pandemic group patients.

In the study, the number of patients in the pandemic group was relatively less (140 *vs.* 163). The reason for the low number of operated patients in the pandemic group was that, in the first four months of the pandemic, a limited number of elective surgeries were performed in the hospital, since the intensive care units were reserved for COVID-19. Also, COVID-19 was a new pandemic, and its consequences were unpredictable, and thoracic surgery was

difficult to manage in the pandemic. It has been observed that in the first 3 months of the pandemic in the USA, individuals diagnosed with cancer decreased by 35-40% and cancer screenings decreased by 60-70%.[13] In Italy, a 36% decrease was noted in the number of patients with NSCLC in the period of June-September 2020.[14] During the pandemic, lung cancer screenings were suspended in many countries due to the risk of infection transmission as well as the false positivity due to infection. This situation was considered likely to cause an increase in the number of patients with advanced stage lung cancer.[15]

Thoracic CT imaging usually reveals bilateral and irregular ground glass opacities in COVID-19 infection, while lesions are unilateral and oval in early-stage lung cancer, but the radiological findings may overlap in some patients.[16] In this study, 5 patients had positive COVID-19 PCR tests at the time of diagnosis, and 6 patients had radiological findings of COVID-19 at diagnosis. These patients were incidentally diagnosed with early-stage lung adenocarcinoma and had mild COVID-19 infection. However, COVID-19 infection can be fatal in lung cancer patients with comorbidities, advanced age, and advanced stage cancer.[17]

In this study, the percentage of T4 tumour and median tumour diameter was significantly lower in patients operated during the pandemic. In China, patients diagnosed with lung cancer during COVID-19 screening had significantly smaller tumour size, and in the study cohort, 80% of patients were at Stage-1 and 55% were females.[12] In South Korea, a significant increase was reported in the rate of lung cancer Stage-3 and stage-4 patients diagnosed during COVID-19.[10] This was thought to be related to the interruption of screening during the COVID-19 period in countries with routine lung cancer screening. In Turkey, there is no routine lung cancer screening method due to the high incidence of tuberculosis and occupational diseases. However, with the COVID-19 pandemic, lung imaging assessment increased significantly, and some individuals were screened, although passively, for lung cancer.

This study had a longer follow-up period than other studies in this field which enabled us to analyse the long-term outcome.[10,18] In the prepandemic group, surgery was performed more frequently on synchronous oligometastatic patients(16 *vs.* 5). The reason for this difference is that surgery of early-stage NSCLC patients was given priority during the pandemic period and definitive CRT option was preferred for oligometastatic NSCLC patients. In Canada, the rate of definitive RT use in the treatment of NSCLC increased in the COVID-19 period, while the rate of CTx and surgical treatment decreased.[19]

In this study, 45% of the patients had SCC and 40% had adenocarcinoma histology, while SCC was the leading histological subtype in both groups. In a study conducted in China, approximately 80% of the patients were reported to have adenocarcinoma histology.[12] The reason for this difference is multifactorial and may be related to the fact that 85% of these patients were either active or former smokers. Previous studies had not investigated the selection of surgical procedures by histological subtype in patients with NSCLC. However, in this cohort, 74% of patients who had pneumonectomy had SCC histology, which was often centrally located (p=0.001). Knowing the histological subtype preoperatively may affect the surgical procedure in the surgical care of NSCLC patients. Today, histological subtype determination in preoperative biopsy can be made at a rate of 70%.[20]

In the prepandemic group, due to longer follow-up, metastasis development was more common, and therefore, the rates of palliative CTx and palliative RT were significantly higher in this group (p=0.005 and p=0.001, respectively). In the pandemic group, neoadjuvant CTx was applied more frequently to patients (Stage-3 patients, in particular) who could not be operated due to the pandemic. In the prepandemic group, the number of patients with T4 tumour, N2 lymph node positivity and definitive RT rate was higher. These findings indicated that the effect of the COVID-19 pandemic on the treatment plan of the operated lung cancer patients was mild, and the treatments were given according to the characteristics of the patient and the cancer. The impact of the pandemic on thoracic cancer treatments in France was often related to the immunotherapy dose modification.[21]

Vaccination rates against COVID-19 and COVID-19 infection rates were significantly higher in the pandemic group. Since the patients in the pandemic group were admitted to the hospital more frequently for treatment during the pandemic period and had risky contacts, they became more infected with the COVID-19 infection. Similarly, in a meta-analysis on this subject, the prevalence of *SARS-CoV-2* infection in lung cancer patients was found to be 15.2%.[22] The high rate of COVID-19 infection despite the high rate of vaccination against *SARS-CoV-2* in the pandemic group has been suggested to be related to the insufficient efficacy of the vaccine in cancer patients receiving active treatment.[23]

In this study, *SARS-CoV-2* positivity was evaluated based on PCR test results. While the PCR test was negative in some of the patients with comorbidities who died during the pandemic period, COVID-19 may have caused the death. In a Canadian study of operated patients, no differences in stage, surgical procedure, or survival were found between the prepandemic and pandemic groups. While the aforementioned Canada study analysed patients for one year, this study analysed patients for two years and the follow-up was longer in the current study.[24] The percentage of patients with T3, T4, N1, N2, and Stage-3 were considerably higher in this cohort when compared to the Canadian study.

In this study, incidentally-diagnosed patients were diagnosed at an earlier stage than patients diagnosed with symptoms, and a significant overall survival advantage was observed in these patients (p=0.008). In the pandemic group, patients were incidentally-diagnosed with NSCLC more frequently (32 *vs.* 15, p=0.001). The increase in the incidentally-diagnosed patients in the pandemic group is likely to be related to increase in thoracic tomography imaging. In this cohort, while the most common histological subtype was SCC in both groups, 72% of the incidentally-diagnosed patients had adenocarcinoma histology. This may be related to the fact that the adenocarcinoma subtype is anatomically in the lung periphery and remains asymptomatic until the late period. In a study, 47% of the patients with NSCLC were diagnosed as a result of incidental scanning, and these patients were younger, had adenocarcinoma histology, and had smaller tumour size.[12] Similarly, the incidentally-diagnosed patients of lung cancer in this study had the opportunity to be diagnosed at younger age with adenocarcinoma histology and at an earlier disease stage. These findings are important for identifying the target population and its routine application in lung cancer screening.

There were certain limitations to this study. The study was unicentric and retrospective, hence the results may not be generalisable to different racial and ethnic populations. However, this study had a longer follow-up period than other studies on this subject, along with comprehensive assessment of patients in all aspects.

CONCLUSION

Significant differences were observed between the prepandemic and pandemic groups of operated NSCLC patients in terms of clinical, pathological, treatment characteristics, and survival outcome. Distant metastasis and mortality rates were higher in the prepandemic group. The frequency of incidental diagnosis was increased in NSCLC patients who were operated during the pandemic period. Incidentally-diagnosed patients often had an early-stage disease with adenocarcinoma histology and better overall survival.

ETHICAL APPROVAL:

An approval was obtained from the Gaziantep University Clinical Research Ethics Committee on 25.05.2022 with the registration No. 2022/143.

PATIENTS' CONSENT:

Informed consents were obtained from the patients and/or their families/legal guardians to publish the data concerning their cases prior to publishing the data.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

HA, AA: Conception and design.
HA, ID: Analysis and interpretation.
HA, ESA, OE: Data collection.
HA, AA, OE: Writing of the manuscript.
HA, ID, AA: Critical revision of the manuscript.
All authors approved the final version of the manuscript to be published.

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