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ABOUT

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Thoracic Research and Practice covers a wide range of topics related to adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery, including diagnostic methods, treatment techniques, and prevention strategies. The journal is interested in publishing original research that addresses important clinical questions and advances the understanding and treatment of these conditions. This may include studies on the effectiveness of different treatments, new diagnostic tools or techniques, and novel approaches to preventing or managing pulmonary diseases.

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Editorial

The Additional Burden of Earthquakes: Asbestos Risks Rising in Türkiye

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Disaster waste can directly and indirectly threaten public health due to the amount and type of waste generated. These waste materials may contain hazardous substances such as pesticides, solvents, and asbestos fibers.[1] Despite being classified as a natural mineral, asbestos has adverse and unnatural health effects on humans. Exposure to asbestos can result in various health issues, such as asbestosis, pleural plaques, pleural thickening, effusion, and cancer. Based on the evidence, exposure to asbestos has been linked to lung, laryngeal, and ovarian cancer, as well as mesothelioma. The World Health Organization stresses that 125 million individuals are subjected to asbestos in their workplaces.[2]

Asbestos is currently used in over 3000 products, which has led to an increase in the risk of occupational and environmental exposure and in the burden of asbestos-related diseases. According to estimates, the "asbestos cancer epidemic" could cause 10 million deaths globally if preventive regulations about asbestos exposure are not implemented. Due to previous exposure to asbestos, it is anticipated that over 200 000 deaths will occur in Europe in the coming decades as a result of mesothelioma.[3] Asbestos leads to a "mutagenic microenvironment" for tissues in the pleura through various mechanisms, such as BRCA1-associated protein-1 mutations.[4] The long latent period of the disease and the lack of treatment options are the challenges. According to the American Cancer Society, the time span between initial exposure and diagnosis typically ranges from 20 to 50 years.[5]

Non-occupational exposure to asbestos is categorized into 4 main groups: exposure to naturally occurring asbestos areas, exposure in the neighborhood area to industrial and mining sources of asbestos, take-home exposure, and home-related exposure.[6] Since asbestos was used as an isolation material in buildings when it was widely used, maintenance, repair, and demolition operations in old buildings may pose a risk of exposure. In this respect, earthquakes can be considered a way of exposure that has the potential to increase the risk of asbestos due to the debris wastes they generate.

In earthquakes, the waste burden is higher than in other types of disasters, as entire buildings become waste. As buildings collapse or damaged ones are demolished, waste is "trapped" in the collapsed or demolished buildings. This can lead to difficulties in separating hazardous waste (e.g., asbestos) from non-hazardous waste (e.g., general construction waste).[1] As the asbestos added cement and was used in many insulation materials in buildings, there is a risk of asbestos fibers being spread through damaged or collapsed buildings after earthquakes.[7-9] This presents a significant threat to public health, so asbestos removal and the management of earthquake debris are essential.[10] Following the earthquake in Kobe in 1995, it is estimated that about 18 million tons of debris, including 11 million tons of concrete, were generated and 26.4 kg of asbestos was released into the environment. Asbestos fibers were detected in the atmosphere in the earthquake area, and asbestos removal costs accounted for 68-94% of the total waste disposal costs.[11]

The asbestos burden was intensified by the February 6 earthquakes in Türkiye, which killed more than 50 000 people and generated 116-200 million tons of rubble.[12] This large quantity of waste from demolitions presents a risk to public health because of asbestos in old buildings. Although there are legal regulations regarding the separation, collection, and disposal of asbestos-containing waste in disaster preparedness plans, there is no information regarding the effectiveness of these measures in the earthquake zone in Türkiye. This increases uncertainty and can lead to problems in risk communication and increased public anxiety about asbestos-related health problems. By contrast, reports issued by the Chamber of Environmental Engineers have detected asbestos in samples obtained from the earthquake zone in April and September 2023.[13,14]

Despite the fact that asbestos was banned in Türkiye in 2008,[15] asbestos is already on Türkiye's agenda due to shipbreaking activities, naturally occurring areas, and the demolition of old buildings in urban renewal projects. According to the "Türkiye

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Asbestos Control Strategic Plan," over 5000 patients were diagnosed with mesothelioma between 2008 and 2012.[16] With the earthquakes that occurred on February 6, 2023, it is foreseeable that Türkiye's asbestos burden will escalate further. Comprehensive measures should be taken to reduce this burden, and Türkiye, as a country with frequent earthquakes, should improve its waste management capacity in disasters, particularly in disaster preparedness plan activities.

Post-earthquake asbestos risk is an additional occupational and environmental risk that should not be ignored. Waste management should be prioritized in disaster preparedness plans. Otherwise, exposure to asbestos can result in severe health problems that have a prolonged impact.

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Original Article

The Epidermal Growth Factor, Anaplastic Lymphoma Kinase, and ROS Proto-oncogene 1 Mutation Profile of Non-Small Cell Lung Carcinomas in the Turkish Population: A Single-Center Analysis

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Abstract

OBJECTIVE: The management of non-small cell lung carcinomas (NSCLC) has changed with the identification of molecular pathways. We aimed to reveal the 3-year epidermal growth factor (*EGFR*), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 (*ROS1*) mutation profile in the Turkish population.

MATERIAL AND METHODS: The histopathological and molecular data of all NSCLC cases from our department between May 2019 and April 2022 were evaluated.

RESULTS: Molecular testing was performed in 197 NSCLC cases, and results were obtained in 182 (92.4%) (M/F: 144/38, aged 39-86). Of these, 121 were diagnosed with adenocarcinoma, 36 with squamous cell carcinoma, and 25 with NSCLC-not otherwise specified. The *EGFR* mutation was seen in 21 (11.5%) cases (6 exon 19 deletions, 3 exon 18 [all codon 719], 2 exon 20, 8 exon 21 point mutations, 1 concurrent exon 19 deletion and exon 20 codon 790 M point mutation, and 1 concurrent exon 19 deletion and exon 21 point mutation). The double mutation rate of *EGFR* was 1.1%. The mean age of these patients was 63.4 (40-79), with 24% of all females (n = 9) and 8.3% of all males (n = 12). The *ALK* mutation was detected in 6 (3.3%) patients (M/F: 4/2, aged 45-82), whereas the *ROS1* mutation was detected in 3 (1.7%) (M/F: 2/1, aged 40-64).

CONCLUSION: It is well established in the literature that *EGFR*-activating mutation rates vary depending on regions and ethnic groups. We concluded that the *EGFR*-activating mutation rates of the Turkish population are similar to the European molecular data instead of the Asian. The *ALK* and *ROS1* mutation rates also seem concordant with the literature.

KEYWORDS: ALK, EGFR, non-small cell lung cancer, mutation profile, ROS1

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INTRODUCTION

Lung cancer is the second most common cancer in the United States, according to Cancer Statistics 2022 data, and constitutes the most common cause of cancer-related death in both genders.[1] Global Cancer Statistics 2020 data estimated around 2.2 million new cases, representing 10% of all cancer cases, and 1.8 million new deaths.[2] The latest Cancer Statistics report published by the Turkish Ministry of Health in 2021 depicted the annual lung cancer rates as 56.7 cases per 100 000 individuals in men, making it the most common cancer in men, and 11.1 per 100 000 individuals in women, ranking fourth in women.[3]

The histopathological classification of lung cancer is divided into 2 broad categories: small cell and non-small cell lung cancer (NSCLC), with the latter representing approximately 85% of all lung cancer cases.[4] The NSCLC has several subtypes, such as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, etc. The management of NSCLCs has changed with the identification of the molecular pathways that are now used in targeted therapies. Testing the presence of driver mutations in specific genes in NSCLCs has affected the clinical management and outcomes of the disease, with recent reports about lung cancer becoming seemingly more favorable in all stages.[5,6]

After the first discovery of overexpression and aberrant activation of the epidermal growth factor receptor (EGFR) in patients with lung adenocarcinoma and several activating mutations of the tyrosine kinase domain of the *EGFR* gene, biological agents called "tyrosine kinase inhibitors" have started to be used in the treatment.[7] Thus, a new era began

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in personalized medicine for NSCLC patients. It is estimated that up to 69% of advanced NSCLC patients have druggable mutations in numerous genes such as *EGFR*, anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*), Kirsten rat sarcoma virus (*KRAS*), V-raf murine sarcoma oncogene homolog B1 (*BRAF*), *MET*, human epidermal growth factor receptor (*HER2*), etc.[8] In current practice, predictive testing for *EGFR* mutations, *ALK, ROS1,* NTRK fusions, and BRAF mutations is recommended to be performed in lung adenocarcinoma regardless of the different risk factors that these patients carry, as only the drugs targeting these molecular alterations have been approved for clinical use.[5]

The incidence rates of these specific mutations vary among different geographical areas, populations, and genders. There have been many reports from Asian and European populations regarding the frequency of these mutations. Türkiye is a country with a unique geographical location between Asia and Europe, and with its multicultural structure, it is home to various ethnic groups. We aimed to reveal the 3-year *EGFR, ALK*, and *ROS1* mutation profiles in the Turkish population in this series and to identify the clinicopathologic characteristics of the mutated cases.

MATERIAL AND METHODS

All NSCLC cases that were evaluated histopathologically and by molecular testing in our department between May 2019 and April 2022 were included in the study. The demographic data of the patients, the type of specimen in which the molecular testing was done (cell block, biopsy, resection), the localization (primary/metastatic) of the specimen in which the molecular testing was done, the histopathological diagnosis, and the mutation rates were noted.

Molecular Analysis

After marking the tumor-rich areas on the hematoxylin-eos in-stained slides, DNA was extracted from 5 paraffin sections (10 µm) representative of the marked tumor tissue using the GeneJET Thermo Scientific extraction kit according to the manufacturer's protocol. The PNAClamp™ *EGFR* Mutation Detection kit (PANAGENE Inc., Korea) was used to detect *EGFR* mutations by real-time polymerase chain reaction (PCR). Real-time PCR reactions of PNA-mediated clamping PCR were performed using an Applied Biosystems™ 7500 Fast and 7500 Real-Time PCR. The *EGFR* mutation types were detected using PNA-mediated real-time PCR. The efficiency of PCR clamping was determined by measuring the threshold cycle (Ct) value. The target somatic mutations included E19 deletions, E21 L858R and L861Q mutations, E18 G719X mutation, E20 S768I mutation, E20 insertions, and E20 T790M mutation.

The fluorescence in situ hybridization (FISH) method was used for ALK and ROS1 translocation using the ZytoLight SPEC ALK and ROS1 Dual Color Break Apart Probe (ZytoVision GmbH, Bremerhaven, Germany). The FISH signal abnormalities were confirmed using a fluorescence microscope with appropriate channels. The signal pattern was evaluated in at least 50 tumor cells as per the standard procedure. If ≥15% split signals and/or loss of green for ALK/loss of orange for ROS1 signals were detected, the test was considered to have yielded a positive result.

This study was performed in line with the principles of the Declaration of Helsinki, and approval was granted by the Ethics Committee of İzmir Katip Çelebi University (Approval number: 2021-GOKAE-0460, date: 2021). Informed consent was obtained from the patients prior to the study.

Statistical Analysis

The results were analyzed using Statistical Package for the Social Sciences Statistics software, version 24.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as the median, and categorical data as percentages. Besides descriptive statistics, the categorical data were compared using the chi-square test. Differences in continuous measurements between the 2 groups were examined by the Student's *t*-test. A *P*-value of <.05 was considered statistically significant.

RESULTS

A total of 197 NSCLC cases underwent molecular analysis. The molecular test results were obtained in 182 (92.4%) of them, with 119 primary lung carcinomas and 63 metastases. There were 144 males (79.1%) and 38 females (20.9%), with a median age of 64 (39-86 years). Molecular testing was not successful in 15 cases because of the inability to retrieve sufficient DNA. These consisted of 7 bone biopsies, 6 cytological specimens, and 2 tissue biopsies with low cellularity.

The molecular testing was performed on biopsies in 106 cases, on cell blocks obtained from cytological specimens in 56 cases, and on resections in 20 cases. The histopathological subtype was adenocarcinoma in 121 cases (66.5%), squamous cell carcinoma (SCC) in 36 cases (19.8%), and NSCLC-Not otherwise specified (NOS) in 25 cases (13.7%).

The *EGFR* mutation was detected in 21 cases, with an overall rate of 11.5% and a median age of 67 (40-79). It was seen more frequently in females with a rate of 23.7% (n = 9), whereas this rate was 8.3% in males (n = 12), and this

Main Points

- The study investigates the molecular mutation profile of non-small cell lung carcinomas (NSCLC) in the Turkish population, focusing on epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (ALK), and ROS oncogene 1 (ROS1) mutations.
- The *EGFR*-activating mutation rates in the Turkish population were found to be similar to European data rather than Asian, with an overall rate of 11.5%.
- The *ALK* and *ROS1* mutation rates in Turkish NSCLC cases were consistent with the literature, with rates of 3.3% and 1.7%, respectively.
- Adenocarcinoma was the most common histological subtype associated with *EGFR* mutations, and *EGFR* mutations were more prevalent in females compared to males.
- These findings underscore the importance of molecular profiling in NSCLC management and highlight the need for personalized therapies targeting specific mutations for improved patient outcomes.

Table 1. Relationship Between Case Characteristics and *Epidermal Growth Factor Receptor* Gene Mutation

			EGFR Gene Mutation Status		
Characteristics		**n (%)**	**Mutated (%)**	**Wild Type (%)**	***P***
Gender	Female	38 (20.9)	9 (23.7)	29 (76.3)	**<.05**
	Male	144 (79.1)	12 (8.3)	132 (91.7)	
Age	Mean ± SD	182 (100)	63.38 ± 9.19	63.71 ± 12.2	.907
	Median (min-max)		67 (40-79)	64 (39-87)	
Histologic diagnosis	Adenocarcinoma	121 (66.5)	19 (15.7)	102 (84.3)	**<.05**
	SCC	36 (19.8)	1 (2.8)	35 (97.2)	
	NSCLC, NOS	25 (13.7)	1 (4)	24 (96)	
Specimen type	Cell blocks (cytology)	56 (30.8)	7 (12.5)	49 (87.5)	.102
	Biopsies	106 (58.2)	9 (8.5)	97 (91.5)	
	Resections	20 (11)	5 (25)	15 (75)	
Sample location	Primary	119 (65.4)	13 (10.9)	106 (89.1)	.722
	Metastatic	63 (34.6)	8 (12.7)	55 (87.3)	
Total		182 (100)	21 (11.5)	161 (88.5)	

EFGR, epidermal growth factor receptor; NOS, not otherwise specified; NSCLC, non-small cell lung carcinoma; SCC, squamous cell carcinoma.

difference was statistically significant (P = .008). The mean age for *EGFR*-mutated cases did not differ statistically from the *EGFR* wild-type cases (63.38 ± 9.19 vs. 63.38 ± 12.20, P = .907).

The mutations were observed in 10.9% (13/106) of primary tumor samples and 12.7% (8/55) of metastatic tumor samples. There was no statistically significant relationship between the tumor samples and *EGFR* mutation presence (P = .722). Also, no significant difference was found between the specimen types (cell blocks, biopsies, and resections) and *EGFR* mutation (P = .102).

The histological subtypes of *EGFR*-mutated cases were as follows: 19 (90.4%) adenocarcinomas, 1 (4.8%) SCC with exon 20 T790M mutation, and 1 (4.8%) NSCLC-NOS with concurrent exon 19 deletion and exon 21 L858R point mutation. The *EGFR* mutation prevalence was significantly higher in

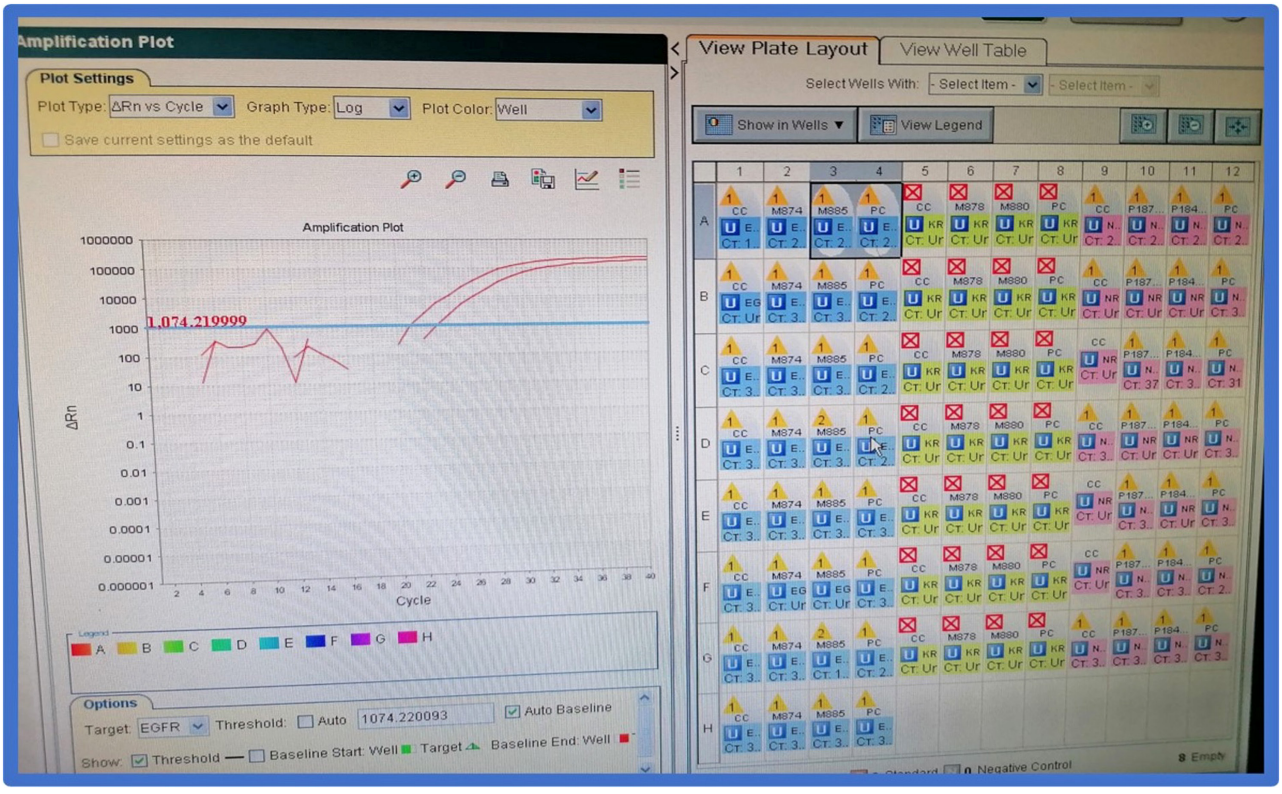


Figure 1. Cycle threshold curve in the real-time polymerase chain reaction analysis result of the case with epidermal growth factor receptor exon 20 T790M mutation.

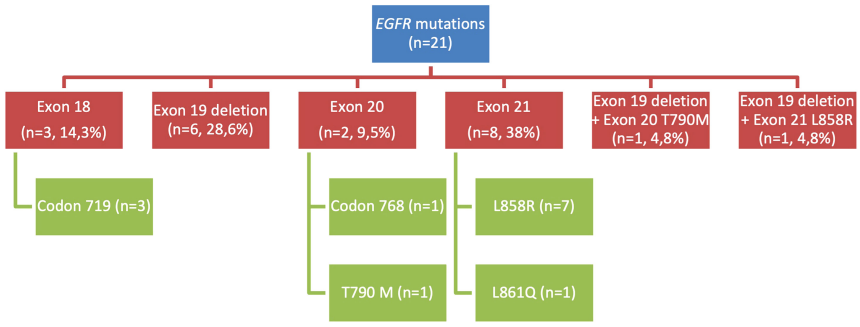


Figure 2. The details and frequencies of *EGFR* gene mutations in each exon. EGFR, epidermal growth factor receptor.

adenocarcinoma cases ($P = .046$). The rate of *EGFR*-mutated adenocarcinomas was 15.7% among all adenocarcinoma cases. The relationship between case characteristics and *EGFR* mutation is given in Table 1.

The most common *EGFR* mutation was detected in exon 21 in 8 cases (38%). The point mutation in this exon was seen in L858R in 7 cases and L861Q in 1 case. This was followed by the exon 19 deletion in 6 cases (28.6%). Other point mutations were detected in exon 18 codon 719 of the gene in 3 cases (14.3%), in exon 20 in 2 cases (9.5%) with a point mutation in codon 768 in 1 case, and in exon 20 T790M in 1 case (Figure 1).

Apart from classical mutation patterns, double mutations were detected in 2 cases (1,1%). Of these, 1 case was diagnosed with NSCLC-NOS, with an exon 19 deletion and an exon 21 codon L858R point mutation. The other case showed an exon 20 codon 790M point mutation with an exon 19 deletion. This case was diagnosed as pulmonary adenocarcinoma metastasis in the liver, and molecular studies were applied to a liver needle biopsy. A case with the EGFR Exon 20 T790M mutation was diagnosed as "NSCLC-primarily compatible with squamous cell carcinoma" from the cell block of a lung transthoracic needle biopsy. The details and the frequencies of *EGFR*-mutated cases in each exon are given in Figure 2.

The *ALK* rearrangement was detected in 6 cases, with an overall rate of 3.3% (Figure 3).

Four of these patients were male, whereas 2 of them were female, and the age range was 45-82. The histological diagnosis was adenocarcinoma in 5 of these cases and NSCLC and NOS in 1. Among the six patients showing rearrangement of the ALK gene, three received the diagnosis from bronchoscopic biopsy, one from endobronchial ultrasound (EBUS) bronchoscopy material, one from transthoracic needle biopsy, and the 48-year-old female ex-smoker patient was

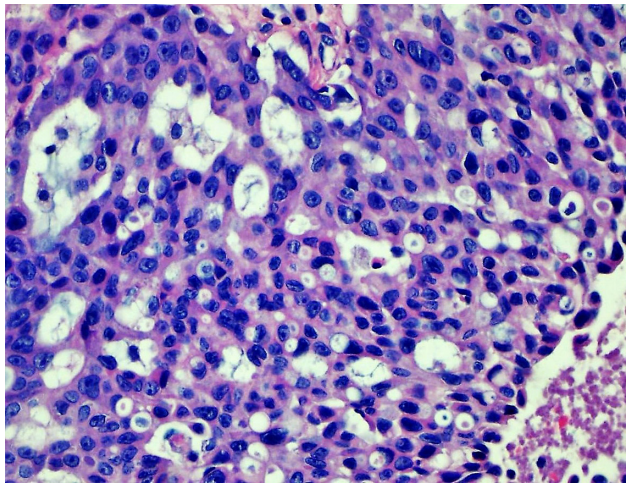


Figure 4. Adenocarcinoma in solid and cribriform pattern in the case showing *anaplastic lymphoma kinase* mutation that was diagnosed from brain metastasis (H&E, X200)

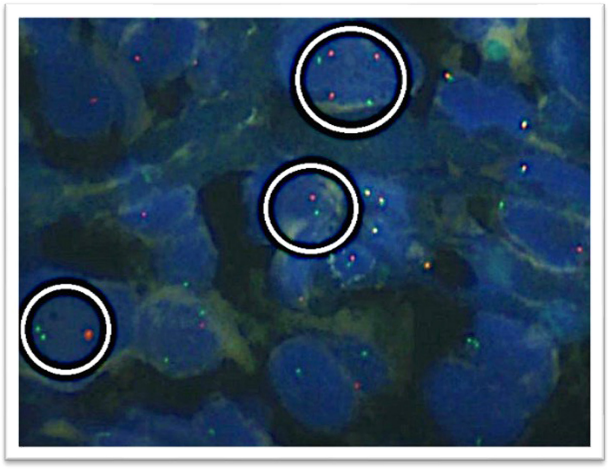


Figure 3. Anaplastic lymphoma kinase fluorescence in situ hybridization-positive case showing split red and green signals detected with anaplastic lymphoma kinase break-apart probe.

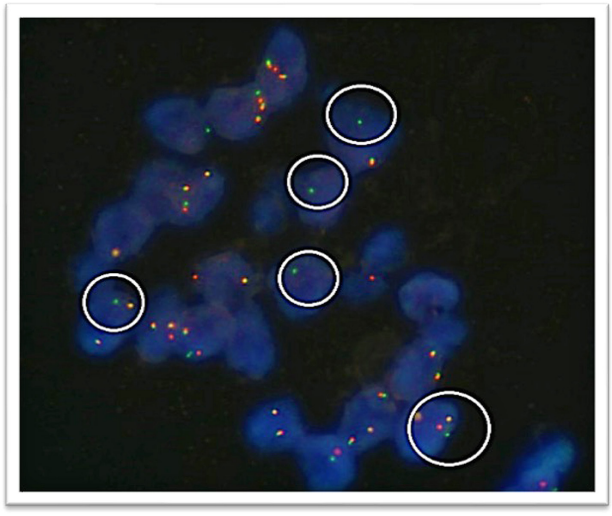


Figure 5. *ROS1* FISH-positive case showing split signals and loss of red signals detected with *ROS1* break-apart probe (*ROS1*: ROS proto-oncogene 1, FISH: Fluorescence in situ hybridization)

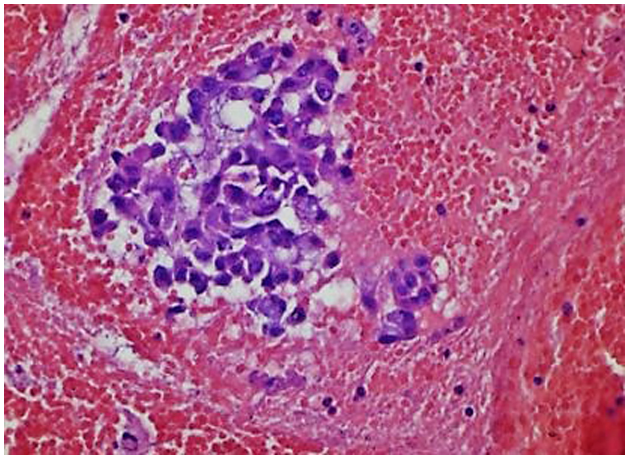


Figure 6. Adenocarcinoma in the cell block in the case showing *ROS proto-oncogene 1* mutation diagnosed from endobronchial ultrasound bronchoscopy material (H&E, X200).

diagnosed with the metastasis specimen from the brain. In the brain metastasis case, the tumor exhibited a solid and cribriform pattern (Figure 4). Three patients were ex-smokers, two were non-smokers, and one was a smoker. ALK gene rearrangement rates in the FISH analysis were observed between 20%-45% (mean 32%).

Three patients harbored *ROS1* rearrangement at an overall rate of 1.7% (Figure 5). Two of them were male, and 1 was female, aged between 40 and 64 years. Two of these tumors were adenocarcinomas, and 1 of them was SCC. The diagnosis of these 3 patients was made from a cell block from EBUS material (Figure 6) in one, an incisional biopsy material from a supraclavicular lymph node in one, and from bronchoscopic biopsy material in one patient. Two patients were diagnosed with adenocarcinoma and one with SCC. In FISH analysis, ROS1 gene rearrangement rates ranged from 25% to 60% (mean 37%). The patient diagnosed with SCC was a 64-year-old male who was diagnosed from a bronchoscopic biopsy. Among the cases, one was an ex-smoker, one was a non-smoker, and one was a smoker patient.

DISCUSSION

As one of the most commonly diagnosed cancers, lung cancer remains the leading cause of death from cancer worldwide. With recent developments regarding the identification of sensitizing mutations in NSCLCs, patients with metastatic disease who did not have a chance at longer survival before might now have more favorable outcomes with the use of targeted, personalized therapies.[9] With this aim, molecular profiling is recommended for all NSCLC patients to be able to decide if they can be candidates for therapies with the so-called "smart drugs."

The *EGFR* is a cell surface protein that encodes a transmembrane protein with an extracellular component that serves as ligand-binding sites. It promotes the autophosphorylation of its tyrosine kinase domain after ligand binding, leading to a molecular cascade of events. The gene is observed to be involved in cell proliferation, decreased apoptosis, angiogenesis, metastasis, and chemoresistance in NSCLCs.[10]

The incidence of *EGFR* mutation depends on different characteristics such as gender, tumor type, smoking history, and ethnic background.[11] The prototype for this is non-smoking, East Asian women with adenocarcinomas, as previously reported by many studies.[12-14] Even though NSCLC incidence is reported to be higher in males, almost all studies that have been published to date have reported a higher frequency of *EGFR* mutation in females. Zhang et al[14] reported the overall female prevalence to be 43.7%, whereas the male prevalence was 24%. In the latest series reported from Türkiye, this rate was observed as 30.5% in females and 7.5% in males.[15] Consistent with these findings, our study revealed a statistically significant difference in terms of gender in *EGFR*-mutated cases, with a female prevalence of 23.7% and a male prevalence of 8.3%.

The *EGFR* mutation prevalences vary between different populations, ethnic groups, and geographic regions. The highest prevalence worldwide has been shown in East Asian populations (up to 59%), whereas the lowest has been reported in European populations (around 10%).[14,16-24] The causes of this discrepancy are still obscure and yet to be defined. With a unique geographical location between Asia and Europe, Türkiye is home to many ethnic groups and populations. The studies from Turkish patient groups have shown a big variation ranging from 4% to 48.1% throughout the years.[15,25-28] The reason for this variation might be the small sample size in the early studies and the use of different methods for the detection of the *EGFR* gene mutation. In the study by Özçelik et al[29] that evaluated the regional distributions of mutations in lung cancer, even though the highest mutation prevalence was observed in the Mediterranean region, the differences were not found to be statistically significant. As a tertiary reference center in the Aegean region in Western Türkiye, the prevalence from our hospital was 11.5%, which was similar to the results of Diniz et al[30] (11.6%) but slightly lower than the results of Calibasi-Kocal et al[25] (16.6%) who reported the prevalence from the same region. The most recent studies with the biggest sample sizes from the central region of Türkiye reported this prevalence to be 16.7% and 16.6%.[15,28] Along with our study, these latest results show that the *EGFR*-activating mutation rates of the Turkish population are similar to the European molecular data instead of the Asian.

In terms of the histological tumor type, *EGFR* mutations are reported to be present in up to 78% of adenocarcinomas in East Asian populations, as opposed to only 10-16% of adenocarcinomas in other ethnicities.[14,16-24] This rate was 20.3% in a comprehensive study from Türkiye that evaluated 959 NSCLC cases.[28] Zhang et al[14] state in their review that adenocarcinoma patients were more likely to harbor *EGFR* mutations, with Asians showing a more striking prevalence than Caucasians. There were a total of 121 adenocarcinoma cases in our series, and 15.7% (n = 19) of them showed an *EGFR* mutation with a statistically significant difference from the other histological subtypes, validating our results being close to the European data once more.

With the extensive research that focused on the activating mutations within the *EGFR* gene, it is now known that

mutations in NSCLCs are limited to the first 4 exons (18-21), and most of the mutations are either point mutations that lead to amino acid substitutions (exons 18 and 21) or in-frame deletions (exon 19).[31] In-frame deletions in exon 19 and L858R point mutations in exon 21 constitute the most powerful predictive biomarkers of response to EGFR tyrosine kinase inhibitor therapy, whereas exon 20 mutations were shown to be associated with a poor response to therapy and increased mortality.[32] In the present study, the most commonly detected mutation type was point mutations in exon 21 (n = 8; 38%) followed by an in-frame deletion in exon 19 (n = 6; 28.6%), which comprised the majority (66.6%) of the mutations in this population. It has been shown that these mutation frequencies can differ in *EGFR* exons owing to the fact that patient populations vary in terms of ethnicity and smoking habits. Exon 20 codon 790M point mutation was observed in 1 of our cases diagnosed with squamous cell carcinoma from a lung transthoracic needle biopsy. The *EGFR* mutations are reported at a rate of 2%-10% in Asian series in squamous cell carcinomas. On a case-by-case basis, adenocarcinomas transforming into squamous cell carcinoma after tyrosine kinase treatment and the presence of EGFR mutations in squamous cell carcinoma in these cases have been reported.[33] However, our case underwent the initial diagnosis and treatment stages in an external center, and the clinical history could not be reached; therefore, no interpretation of the transformation could be made.

Double mutation patterns have also been shown in NSCLC patients, with prevalence rates ranging from 0.47% to 7%.[32,34] Even though the data on the clinical characteristics of these cases are limited in the literature, in the study by Wei et al[32] that assessed 32 patients with double mutations in the *EGFR* gene, the response rate to therapy was found to be lower compared to patients who showed single mutations. The double mutation rate in our study was 1.1%, and the mutated genes were exon 19 deletion and exon 21 L858R in 1 case, and exon 19 deletion and exon 21 L858R point mutation in the other.

Due to the increase in genetic alterations with age, oncogenic mutations are more likely to be seen in the elderly. In patients with tumors harboring *EGFR* mutations, the mean age is reported to be around 60-65 years. Older age has been associated with a higher EGFR mutation rate in NSCLCs.[28,34] The median age in our study was 64, and we could not demonstrate a significant relationship between the presence of an *EGFR* mutation and age.

e *ALK* gene encodes a tyrosine kinase transmembrane protein and consists of 30 exons mapping to the long arm of chromosome 2. After the discovery of *EGFR* mutations, a novel transforming fusion gene resulting from the linkage between the echinoderm microtubule-associated protein-like 4 (EML4) and *ALK* genes in NSCLCs has been identified. It was elucidated that the resulting chimera proteins from this fusion have accelerated tyrosine kinase activity, which results in potent oncogenic effects. This fusion is reported to be seen at varying rates in NSCLCs throughout the world, ranging from 1% to 10%, is more prevalent in younger adults (in the fourth or fifth decades) compared to *EGFR* mutations, and is typically detected in adenocarcinomas with solid patterns.[9] Our study's ALK rearrangement rate was 3.3% with 6 cases (5 adenocarcinomas, 1 NSCLC, NOS). Two of the patients were under 50 years old, 3 were ex-smokers, and 2 were non-smokers. In the majority of cases (5 out of 6), the histopathological type was adenocarcinoma, consistent with the literature. In the patient diagnosed with brain metastasis, the metastatic pattern was solid and cribriform.

ROS1 is a gene that acts as an orphan tyrosine kinase receptor, and even though it has functional and structural similarities to the *ALK* gene, it has a unique extracellular domain, and little is known about its function. Its frequency is similar worldwide, with an estimated overall prevalence of 1.9% ranging from 0.9% to 2.6% in different studies. Just like *ALK*, rearrangements in this gene are seen more frequently in women, non-smokers, and younger ages.[9] We detected 2 cases with *ROS1* rearrangement, with an overall rate of 1.7%, which is consistent with the literature data. The youngest patient was a 40-year-old female who was an ex-smoker. Two patients had adenocarcinoma, whereas unexpectedly, the other case was a SCC. The SCC diagnosis was given from a bronchoscopic biopsy and the patient was a 64-year-old male. In the literature, rearrangements of the ROS1 gene are reported as quite rare in SCCs. Since our case received the diagnosis from a bronchoscopic biopsy, the possibility of an accompanying adenocarcinoma component cannot be ruled out.

Molecular profiling in NSCLCs is performed routinely in Türkiye in most centers. However, in 5%-25% of the cases retrieved for molecular studies, poor-quality biopsies and an insufficient amount of tumor cells cause the testing to be unsuccessful.[35] This rate was 7.8% in our study with 15 cases. To obtain better results in molecular testing, tissue processing and handling should be done very carefully.

A limitation of our study is that, because our hospital is a tertiary reference center, most of the cases were brought from other centers only for molecular testing. Therefore, the data on the smoking history and clinical symptoms and signs could not be obtained in most of them, and the association between smoking and mutation presence could not be assessed. However, detailed and good-quality molecular analysis along with confirmed histopathological diagnoses constitute the strong point of our study.

In conclusion, it is well established in the literature that *EGFR*-activating mutation rates vary depending on regions and ethnic groups. Our study showed that the *EGFR*-activating mutation rates of the Turkish population are similar to the European molecular data instead of the Asian. Comprehensive studies on mutation incidences report a substantial lack of data from several large geographic regions of the world, including our region, and we believe that our findings will contribute to the literature in this context.

Ethics Committee Approval: This study was approved by Ethics committee of İzmir Katip Çelebi University (Approval number: 2021-GOKAE-0460, date: 2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.G., I.E.C.; Design – E.G., I.E.C.; Supervision – I.E.C.; Resource – I.E.C., U.O., H.E., B.S.; Materials – I.E.C., U.O., H.E., B.S.; Data Collection and/or Processing – E.G., I.E.C., U.O., H.S., B.S.; Analysis and/or Interpretation – I.E.C., B.S.; Literature Search – E.G., I.E.C.; Writing – E.G., I.E.C.; Critical Review – I.E.C.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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Original Article

Tobacco Use Status of Medical Faculty Students and Evaluation of Affecting Factors

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Abstract

OBJECTIVE: The aim of the study is to determine the tobacco use status of first and fifth grade students studying at Dokuz Eylül University Faculty of Medicine in the 2022-2023 academic year and to evaluate the factors affecting tobacco use.

MATERIAL AND METHODS: The data of the cross-sectional study were obtained by sending a form prepared in electronic environment to the students after a brief information was given in the unit/classroom where they did their internship, and the students responded on their mobile phones. In research, 539 of 790 students answered the form.

RESULTS: The prevalance of tobacco use was 34.1% (first: 29.8%, fifth: 40.8%) (female: 26.7%, male: 40.4%). According to multivariate analysis, tobacco use in first grades increases 1.8 times (95% CI: 1.1-3.3) if the general health perception is moderate/poor, 2.9 times (95% CI: 1.2-6.8) to be exposed to insistence of friends for tobacco use, 2.4 times (95% CI: 1.3-4.3) for at least one of the family members to use tobacco, 29.7 times (95% CI: 3.9-224.1) for at least one of the close friends to use tobacco, and 3.9 times (95% CI: 2.2-7.1) not to think that physicians should set an example for the society by not using tobacco; in fifth grade, tobacco use by at least one of the close friends increases 9.6 times (95% CI: 2.1-43.6), and not thinking that physicians should set an example for the society by not using tobacco increases 4.9 times (95% CI: 2.7-9.2).

CONCLUSION: In research, it is seen that tobacco use is common among medical faculty students, and the prevalance of use increases as they get higher classes.

KEYWORDS: Tobacco use, cigarette smoking, students, medical, affect
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INTRODUCTION

Tobacco epidemic is one of the biggest public health threats, which is among the leading causes of preventable disease, disability, and death.[1,2] One out of every 2 tobacco users dies due to tobacco-related diseases, which means that more than 8 million people die annually, 7 million of whom are directly and 1.2 million are due to passive exposure (65 000 children).[2] According to the World Health Organization (WHO) reports, the prevalence of tobacco use in the global adult population, which was 23.6% in 2018 (female: 16.2%, male: 49.3%), decreased to 22.3% in 2020 (female: 7.8%, male: 36.7%) and it is projected to decrease to 20.9% by 2025.[3,4] The increase in use among young people (especially adolescent girls) in recent years raises concerns.[5] According to the Global Adult Tobacco Survey, which was recently published in Türkiye, the prevalence of tobacco use in adults in 2016 was 31.6% (female: 19.2%, male: 44.1%).[6] According to the Türkiye Health Survey 2019, the rate of individuals aged 15 and over who use tobacco every day is 28%, while the rate of occasional users is 3.4%.[7] According to the WHO report, 30.7% of adults in Türkiye use tobacco in 2020.[4] Starting to use tobacco usually occurs during adolescence/young adulthood, and university life coincides with this period.[8] It has been stated that university years are a risky period for tobacco use due to negative situations such as leaving home and family, adapting to a new environment, educational problems, and being a candidate for a profession.[9] It is seen that tobacco use among medical students is a common and important problem as it is in society. According to studies in the last decade, the prevalence of tobacco use among medical students in Türkiye is 9.3%-33.0% (female: 3.9%-28.8%, male: 17.7%-42.0%), while it is 2.2%-38.8% (female: 0.0%-28.1%, male: 3.2%-58.6%) abroad.[10-17] In the literature, it is seen that medical students who do not use tobacco feel more responsible for tobacco cessation, provide more counseling, and physicians with better health behaviors are more effective in cessation counseling. In this context, in the fight against tobacco, it is important to know the tobacco use status of medical students as future physicians and the reasons for their use because they play an important role in quitting tobacco, have leadership qualities in tobacco control, and are role models for society.[18,19] The aim of this study is to determine the tobacco use status of first- and fifth-grade students studying at Dokuz Eylül University Faculty of Medicine (DEUFM) in the 2022-2023 academic year and to evaluate the factors affecting tobacco use.

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MATERIAL AND METHODS

Study Design and Sample Size

The population of this cross-sectional study consists of first- and fifth-grade students studying at DEUFM in the 2022-2023 academic year. There are 790 students in total, 453 of whom are in the first grade and 337 in the fifth grade. It was aimed to reach the whole universe without choosing a sample, and a total of 539 students (reach rate: 68.2%), including 326 students from the first grade and 213 students from the fifth grade, participated in the research. Voluntary participation was ensured by informing the students about the study, and their consent was obtained by a form in an electronic environment. The data of the research were collected in November-December of 2022.

Questionnaire

As a data collection tool, a questionnaire form prepared in an electronic environment by the researchers using the literature was used. The questionnaire form consists of 48 questions and sub-questions. In the first part, there are 31 questions with variables such as sociodemographic, body, and health status characteristics of students, tobacco use status of family members, close friends, and students. In the second part, students who regularly/occasionally use any tobacco product answered 11 questions about tobacco use characteristics, and the Fagerstrom Test for Nicotine Dependence consists of 6 questions to determine the level of dependence. The answers to questions in the dependency test are scored from 0 to 1 or from 0 to 3. According to the Fagerstrom score, it is classified as 0-2 points very low, 3-4 points low, 5 points moderate, 6-7 points high, and 8-10 points very highly dependent.[20] The shareable link of the form was sent to students in the unit/classroom where they did their internship, after a brief information was given by the researcher, via class/internship WhatsApp groups, and students were expected to answer the form on their mobile phones.

Definitions

Students who regularly or occasionally use any tobacco product are defined as "tobacco users," while students who have quit or never use are defined as "tobacco non-users".

Ethics Committee Approval

The necessary permission was obtained from DEU Dean's Office in April 2022. Ethics committee approval was obtained with the decision numbered 2022/35-10 on November 2, 2022 from the Non-Interventional Research Ethics Committee of DEU.

Main Points

- Tobacco use is common among medical faculty students, and the prevalence of use increases as they get higher in classes.
- Tobacco use of close friends and family members is an important risk factor for medical students' tobacco use.
- The awareness of medical students who are prospective physicians about their position in tobacco control should be increased.
- Non-cigarette tobacco products should not be ignored in tobacco control.

Statistical Analysis

Statistical Package for the Social Sciences 24.0 (IBM Corp., Armonk, NY, USA) was used in data analysis. Descriptive findings were presented as number, percentage, mean ± SD, and median (minimum–maximum value). Chi-square, Fisher–Freeman–Halton (post hoc Bonferroni test), Fisher's exact test, and *t*-test as univariate analysis to determine the relationship of independent variables with tobacco use. Logistic regression analysis (enter method) was used as multivariate analysis. Logistic regression analysis results are presented with OR and 95% CI. The significance level of $P < .05$ was accepted for statistical tests.

RESULTS

Of the 539 participants, 326 (60.5%) were first grade students and 213 (39.5%) were fifth grade students. Out of the total, 292 (54.2%) were male and 247 (45.8%) were female. The mean age of first graders is 18.89 ± 1.31, with a median age of 19 (17-27); mean age of fifth graders is 22.93 ± 1.14, with a median age is 23.[21-29] The sociodemographic, body, and health status characteristics of the research group are given in Table 1.

In research, 42.1% of students (first: 42.6%, fifth: 41.3%) have habit of doing any sport and 37.7% of them (first: 41.1%, fifth: 32.4%) are involved in any branch of art. Students who are exposed to friends' insistence for tobacco use are 8% (first: 8.3%, fifth: 7.5%). The majority of students have good communication with their family and friends. The rate of those who have moderate/poor communication with family is 23.3% in first graders and 18.3% in fifth graders; the rate of those who have moderate/poor communication with friends is 25.4% in first graders and 19.7% in fifth graders.

More than half of participants (57.3%) tried to use tobacco (first: 49.1%, fifth: 70%). First try age is 15.73 ± 2.68 (minimum: 6, maximum: 21) for first graders, 16.49 ± 3.19 (minimum: 4, maximum: 23) for fifth graders. The most common reasons for both first and fifth grade students who have never tried tobacco use are that it is harmful to health, dislikes its smell or smoke, and does not attract attention. Incompatibility with profession of medicine and the idea of being good example for the environment as a health worker are among the reasons why approximately one-third of students do not try. Not disturbing/harming others (31.3% vs. 14.5%), not being welcomed by the environment (14.4% vs. 8.1%), family reaction (30.0% vs. 14.5%), and friends reaction (8.1% vs. 4.8%) in the first grades; opinions about the tobacco industry (22.6% vs. 13.1%), and finding it contrary to beliefs (17.7% vs. 14.4%) were stated as reasons for not trying at a higher rate in fifth grades (Figure 1).

The prevalence of tobacco use among students was 34.1% (cigarette: 28%, hookah: 14.7%, e-cigarette: 3.7%, other tobacco products: 6.3%). The prevalence of tobacco use in first grades was 29.8%, it is 40.8% in fifth grades (Table 2). At least one of family members of 54.7% of students (first:

Table 1. Sociodemographic and Body and Health Status Characteristics of the Research Group

Sociodemographic and Body and Health Status Characteristics (n = 539)		First Grade		Fifth Grade		Total	
		n	%	n	%	n	%
Gender	Female	148	45.4	99	46.5	247	45.8
	Male	178	54.6	114	53.5	292	54.2
Marital status	Married	1	0.3	1	0.5	2	0.4
	Single	325	99.7	212	99.5	537	99.6
Perception of economic status	Income < expenses	39	12.0	33	15.5	72	13.4
	Income = expense	188	57.7	126	59.1	314	58.2
	Income > expenses	99	30.3	54	25.4	153	28.4
Working status	Working	9	2.8	16	7.5	25	4.6
	Not working	317	97.2	197	92.5	514	95.4
Scholarship status	Yes	83	25.5	101	47.4	184	34.1
	No	243	74.5	112	52.6	355	65.9
Place of residence during medical education*	Dormitory	199	61.0	43	20.2	242	44.9
	Alone	36	11.0	49	23.0	85	15.8
	With family	48	14.7	38	17.8	86	16.0
	With relative	8	2.5	3	1.4	11	2.0
	With friend	45	13.8	116	54.5	161	29.9
Residence of the family	Rural area	38	11.7	20	9.4	58	10.8
	Urban area	288	88.3	193	90.6	481	89.2
Family structure	Nuclear family	288	88.3	189	88.7	477	88.5
	Separated parents	11	3.4	13	6.1	24	4.5
	Extended family	22	6.8	7	3.3	29	5.4
	Other	5	1.5	4	1.9	9	1.6
Mother's education status	Illiterate	13	4.0	9	4.2	22	4.1
	Literate	9	2.8	5	2.4	14	2.6
	Primary school	53	16.3	36	16.9	89	16.5
	Secondary school	23	7.0	16	7.5	39	7.2
	High school	73	22.4	45	21.1	118	21.9
	University	153	46.9	102	47.9	255	47.3
	Don't know	2	0.6	0	0.0	2	0.4
Father's education status	Illiterate	1	0.3	1	0.5	2	0.4
	Literate	3	0.9	5	2.3	8	1.5
	Primary school	34	10.4	23	10.8	57	10.6
	Secondary school	30	9.2	14	6.6	44	8.2
	High school	60	18.5	38	17.8	98	18.2
	University	195	59.8	132	62.0	327	60.6
	Do not know	3	0.9	0	0.0	3	0.5
Body mass index	Underweight	36	11.0	17	8.0	53	9.8
	Normal	212	65.0	141	66.2	353	65.5
	Overweight	67	20.6	44	20.7	111	20.6
	Obese	11	3.4	11	5.2	22	4.1
Body perception	Underweight	44	13.5	22	10.3	66	12.2
	Normal	219	67.2	148	69.5	367	68.1
	Overweight	62	19.0	39	18.3	101	18.8
	Obese	1	0.3	4	1.9	5	0.9

(*Continued*)

Table 1. Sociodemographic and Body and Health Status Characteristics of the Research Group (*Continued*)

Sociodemographic and Body and Health Status Characteristics (n = 539)		First Grade		Fifth Grade		Total	
		n	%	n	%	n	%
General health perception	Very good	20	6.1	16	7.5	36	6.7
	Good	119	36.5	93	43.7	212	39.3
	Moderate	138	42.3	74	34.7	212	39.3
	Poor	44	13.4	27	12.7	71	13.2
	Very poor	5	1.5	3	1.4	8	1.5
Presence of chronic disease	Yes	19	5.8	46	21.6	65	12.1
	No	307	94.2	167	78.4	474	87.9
Total		326	100.0	213	100.0	539	100.0

*Multiple responses.

51.8%, fifth: 59.2%) and at least one of close friend of 82.2% of students (first: 77.9%, fifth: 88.7%) used tobacco.

Almost all students (98.1%) had previously received information about the harms of tobacco. The most common information sources for first are internet (80.3%), school (73.6%), television (69.1%), and family (64.0%); in fifth grade, they are the internet (84.9%), health workers (84.9%), school (81.1%), and television (74.5%). The least chosen answer as information was friend (with 40.4% and 49.5% respectively).

In research, 95.1% of first graders and 99.5% of fifth graders are exposed to tobacco smoke at various frequencies. The rate of those who are frequently/always exposed is 31.9% in first graders and 40.8% in fifth graders. The rate of students who think that physicians should set an example for society by not using tobacco is 70.9% (first: 71.5%, fifth: 70.0%).

Of students who regularly use tobacco, 59.4% started using it before entering medical faculty. Of fifth grade students who started smoking regularly in faculty, 50% started in first grade, 18.4% in second grade, 2.6% in third grade, 21.1% in fourth grade, and 7.9% in fifth grade. Five first-grade students start to use tobacco regularly after entering faculty. The tobacco use characteristics of students are shown in Table 3.

The median Fagerstrom score was 3 (first: 2, fifth: 3). While the rate of first graders who are highly/very highly dependent is 12.0%; the rate of fifth graders is 19.6%.

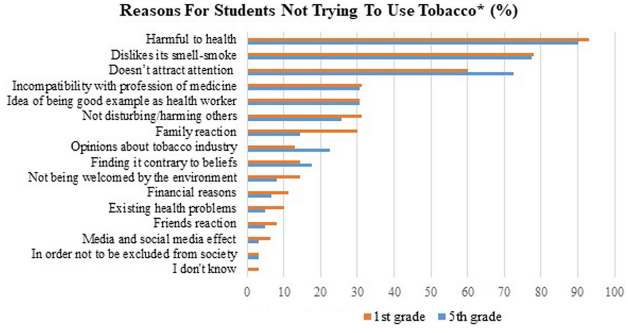


Figure 1. Reasons For Students Not Trying To Use Tobacco. *Multiple response.

In research, 75.6% of students plan to quit using tobacco (first: 65.0%, fifth: 88.0%). One-third of those who have a quit plan are considering quitting within the next month. In the research group, 76.1% of students received information about quitting methods (first: 69.8%, fifth: 83.3%) and 60.7% of students tried to quit in the last 12 months. The most common method used by those trying to quit is self-cessation (93.9%). The second method most frequently used by first graders is consultancy from health institutions (5.6%) and nicotine replacement treatments (9.1%) in fifth graders.

The most common reasons for students to start using tobacco are reducing distress-stress, enjoying, curiosity, and seeing it as a means of entertainment in both first and fifth graders. While the influence of close friends/environment (31.6% vs. 18.8%), school problems (38.6% vs. 6.3%), personal-family problems (21.1% vs. 15.6%), socializing (19.3% vs. 9.4%), attention raising (24.6% vs. 3.1%), and weight control (8.8% vs. 3.1%) were stated to be reasons for starting at a higher rate in fifth grades; emulation-enthusiasm (28.1% vs. 22.8%) and seeking new pleasures (18.8% vs. 14.0%) were shown as reasons at a higher rate in first graders (Figure 2).

While the prevalence of use of hookah (female: 6.9%, male: 21.2%) and other tobacco products (female: 1.2%, male: 10.6%) was significantly higher in males than in females ($P < .001$); there is no significant difference between genders for cigarette and e-cigarette use ($P = .077$). The prevalence of cigarette smoking was significantly higher in fifth grade students (32.9%) than in first graders (24.8%) ($P = .043$). The prevalence of e-cigarette use was significantly higher in first grade students than in fifth graders ($P = .006$). There was no significant difference according to class in terms of the prevalence of use of hookah and other tobacco products. Univariate analyses showing the relationship of independent variables with tobacco use are shown in Table 4.

According to multivariate analysis, tobacco use by at least one of close friends and not thinking that physicians should set an example for society by not using tobacco in fifth grade, in addition to moderate/poor general health perception, the insistence of friends to use tobacco, and tobacco use by at least one of family members were the factors affecting tobacco use in first grade (Table 5).

Table 2. Tobacco Use Status of Medical Faculty Students and Their Family Members

	First Grade									
	Tobacco		Cigarette		Hookah		E-Cigarette		Other Tobacco Products	
Tobacco Use Status (n = 326)	n	%	n	%	n	%	n	%	n	%
Student										
Regularly	97	29.8	37	11.4	0	0.0	2	0.6	0	0.0
Occasionally			44	13.5	46	14.1	16	4.9	25	7.7
Ex	229	70.2	17	5.2	10	3.1	4	1.2	2	0.6
Never			228	69.9	270	82.8	304	93.3	299	91.7
Mother										
Yes	68	20.9	66	20.2	0	0.0	1	0.3	1	0.3
No	258	79.1	260	79.8	326	100.0	325	99.7	325	99.7
Father										
Yes	114	35.0	110	33.7	5	1.5	7	2.1	6	1.8
No	212	65.0	216	66.3	321	98.5	319	97.9	320	98.2
Sibling										
Yes	65	19.9	62	19.0	11	3.4	7	2.1	3	0.9
No	261	80.1	264	81.0	315	96.6	319	97.9	323	99.1
Total	326	100.0	326	100.0	326	100.0	326	100.0	326	100.0
	Fifth Grade									
	Tobacco		Cigarette		Hookah		E-Cigarette		Other Tobacco Products	
(n = 213)	n	%	n	%	n	%	n	%	n	%
Student										
Regularly	87	40.8	37	17.4	0	0.0	0	0.0	0	0.0
Occasionally			33	15.5	33	15.5	2	0.9	9	4.2
Ex	126	59.2	23	10.8	26	12.2	4	1.9	9	4.2
Never			120	56.3	154	72.3	207	97.2	195	91.6
Mother										
Yes	47	22.1	47	22.1	0	0.0	0	0.0	0	0.0
No	166	77.9	166	77.9	213	100.0	213	100.0	213	100.0
Father										
Yes	81	38.0	81	38.0	0	0.0	0	0.0	3	1.4
No	132	62.0	132	62.0	213	100.0	213	100.0	210	98.6
Sibling										
Yes	62	29.1	59	27.7	3	1.4	4	1.9	0	0.0
No	151	70.9	154	72.3	210	98.6	209	98.1	213	100.0
Total	213	100.0	213	100.0	213	100.0	213	100.0	213	100.0

DISCUSSION

In this study, the tobacco use status of the first and fifth grade students of DEUFM and the affecting factors were evaluated. The tobacco use prevalence of the medical students was 34.1% (cigarettes: 28%, hookah: 14.7%, e-cigarettes: 3.7%, other tobacco products: 6.3%). The prevalence of tobacco use among first grade students was 29.8%, while it was 40.8% in fifth grade students. While the prevalence of use among female students is 26.7% and 40.4% among male students.

Tobacco use prevalence was 27% at Mustafa Kemal University in 2017 (first grade: 15.8%, fourth grade: 35%, last grade:33.3%); it was 28.2% at Düzce University in the 2019-2020 academic year.[13,21] In a study in Northern Cyprus in the 2018-2019 academic year, the prevalence of cigarette smoking was 33.7% (first: 28.9%, fifth: 35.5%), and the prevalence of the use of non-cigarette tobacco products was 26.8%.[22] In a study in Malaysia in 2021, the prevalence of tobacco use was 10.3% (cigarettes: 4.7%, hookah: 4%, e-cigarettes: 6.4%).[23] The prevalence of tobacco use in this study seems to be higher than in other studies. It is thought that the

Table 3. Tobacco Use Characteristics of Students Who Use Tobacco in the Research Group

	First Grade		Fifth Grade		Total	
	Mean (SD)	Median (Minimum–Maximum)	Mean (SD)	Median (Minimum–Maximum)	Mean (SD)	Median (Minimum–Maximum)
Age to start smoking cigarettes regularly (n = 74)	17.2 (1.6)	17 (13-20)	18.8 (2.0)	19 (13-23)	18 (2)	18 (13-23)
Number of cigarettes used per day (n = 74)	13.8 (7.2)	15 (1-30)	17.0 (12.4)	15 (4-80)	15.4 (10.2)	15 (10-80)
Smoking cigarette duration (pack-years) (n = 97)	1.5 (2.1)	0.5 (0.1-10.4)	3.8 (5.0)	2.5 (0.1-32.0)	2.6 (3.9)	1.5 (0.1-32.0)
Age to start using e-cigarettes regularly (n = 2)	17.5 (0.7)	17.5 (17-18)	-	-	17.5 (0.7)	17.5 (17-18)
Age of starting to use hookah (n = 40)	16.2 (1.4)	16 (13-19)	17.0 (2.6)	18 (12-20)	16.5 (1.9)	16.5 (12-20)
The amount of hookah sessions consumed per week (n = 24)	0.2 (0.4)	0.1 (0.01-1.0)	0.4 (0.4)	0.3 (0.1-1.0)	0.3 (0.2)	0.2 (0.1-1.0)

higher rate of males in this study compared to other studies and the prevalence of the use of other tobacco products may cause this situation. The prevalence of cigarette smoking was similar to many other studies. It is thought that the variable frequencies seen in different studies are due to the place of work, research group, sociocultural–economic differences, variations in tobacco use definitions, and legal regulations differences. It is seen that the use of non-cigarette tobacco products has also become widespread over the years, and non-cigarette tobacco products are given more place in studies abroad compared to our country. In the study at Yıldırım Beyazıt University in 2021, the prevalence of cigarette smoking among medical students was 17.2%; (hookah: 20.5%, pipe: 12.6%, cigar: 7.5%, e-cigarette: 3.7%).[24] These findings show that non-cigarette tobacco products should also be taken into account in tobacco control programs. In this study, the prevalence of use by females was higher than in many other studies. This situation is thought to be a reflection of the recent increase in usage, especially among young women. In studies of different years among medical students, it is observed that the prevalence of tobacco use has increased as they get higher in classes. Similar to this study, in a study at 3 medical faculties (Dokuz Eylül, Karadeniz Technical, Yüzüncü Yıl), the smoking of last grade students was 2.71 times higher than that of first graders; in a study in Syria, tobacco use in -grade students was 2.75 times more than in first graders.[25,26] The inadequacy of education about tobacco in faculty, anxiety/stress experienced during education, change in the social environment, increase in the intensity of work in clinics as graduation approaches, specialization exam and anxiety about the future may have contributed to this situation. It is thought that medical education and especially clinical practices do not have a sufficient effect on preventing the initiation of tobacco use and enabling users to quit. In this study, it is seen that the use of e-cigarettes in first grades is significantly higher than in fifth grades. This finding can be considered as data supporting the harm reduction strategy of the tobacco industry. The tobacco industry's continued active work is one of the most difficult barriers in the fight against tobacco.

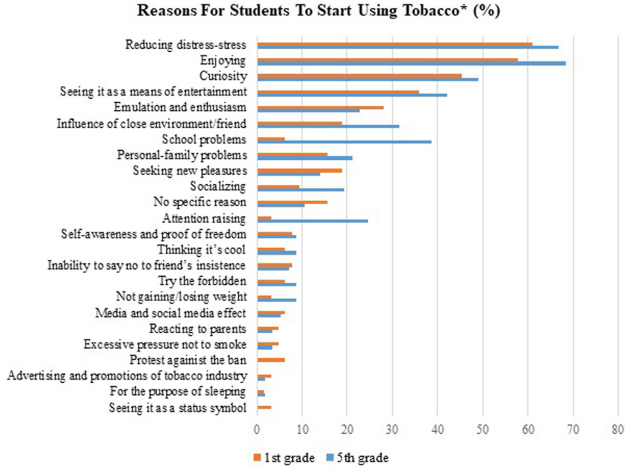


Figure 2. Reasons For Students To Start Using Tobacco. *Multiple responses.

In order to prevent medical students from using tobacco, it is necessary to know the reasons for starting to use tobacco and not trying to use it. In literature, the reasons that come to the forefront in studies both in our country and abroad are the influence of the close environment/friend, curiosity, and stress. In this study, reducing distress–stress, which is the most common reason for starting to use tobacco, and the influence of the close environment/friend, which is the reason for starting a quarter of students, are at the top of the list in many other studies, although the rate varies. It is seen that the reasons for not trying and not using it are not examined much in studies both in our country and abroad. However, the reasons for not trying are as important a guide as the reasons for starting tobacco use in preventing and quitting smoking. In this study, it was seen that the most common reasons for not trying to use tobacco were that it was harmful to health, they disliked its smell and smoke, and that it did not attract attention. Only one-third of those who did not try to use tobacco stated that they did not try it because they thought that it was not compatible with the profession of medicine and that they should be a good example for the environment as a health worker. This situation shows

Table 4. Tobacco Use Status by Various Characteristics of the Research Group

		First Grade					Fifth Grade					Total				
		Tobacco Use					Tobacco Use					Tobacco Use				
		Yes		No			Yes		No			Yes		No		
Variables (n = 539)		**n**	**%**	**n**	**%**	***P***	**n**	**%**	**n**	**%**	***P***	**n**	**%**	**n**	**%**	***P***
Gender	Female	32	21.6	116	78.4	.003*	34	34.3	80	65.7	.072*	66	26.7	181	73.3	.001*
	Male	65	36.5	113	63.5		53	46.5	46	53.5		118	40.4	174	59.6	
Perception of economic status	Income < expenses	14	35.9	25	64.1	.661*	18	54.5	15	45.5	.214*	32	44.4	40	55.6	.131*
	Income = expenses	55	29.3	133	70.7		49	38.9	77	61.1		104	33.1	210	66.9	
	Income > expenses	28	28.3	71	71.7		20	37.0	34	63.0		48	31.4	105	68.6	
Working status	Working	5	55.6	4	44.4	.133*	9	56.3	7	43.7	.192*	14	56.0	11	44.0	.018*
	Not working	92	29.0	225	71.0		78	39.6	119	50.4		170	33.1	344	66.9	
Scholarship status	Yes	27	32.5	56	68.5	.522*	36	35.6	65	64.4	.142*	63	34.2	121	65.8	.971*
	No	70	28.8	173	71.2		51	45.5	61	54.5		121	34.1	234	65.9	
Place of residence during medical education	Dormitory	56	28.1	143	71.9	.215**	17	34.7	32	65.3	.006**	73	29.4	175	70.6	.001**
	Alone	9	25.0	27	75.0		28	58.3	20	41.7		37	44.0	47	56.0	
	With family/relative	14	25.5	41	74.5		9	23.1	30	76.9		23	24.5	71	75.5	
	With friend	19	42.2	26	57.8		51	45.1	62	54.9		70	44.3	88	55.7	
Residence of the family	Rural area	7	18.4	31	81.6	.104*	9	45.0	11	55.0	.691*	16	27.6	42	72.4	.265*
	Urban area	90	31.3	198	68.7		78	40.4	115	59.6		168	34.9	313	65.1	
Family structure	Nuclear family	84	29.2	204	70.8	.523*	76	40.2	113	59.8	.598*	160	33.5	317	66.5	.420*
	Others	13	34.2	25	65.8		11	45.8	13	54.2		24	38.7	38	61.3	
Mother's educaiton status	Secondary school and below	39	39.8	59	60.2	.011*	25	37.9	41	62.1	.555*	64	39.0	100	61.0	.123*
	High school and above	58	25.7	168	74.3		62	42.2	85	57.8		120	32.2	253	67.8	
Father's educaiton status	Secondary school and below	25	36.8	43	63.2	.153*	16	37.2	27	62.8	.587*	41	36.9	70	63.1	.486*
	High school and above	71	27.8	184	72.2		71	41.8	99	58.2		142	33.4	283	66.6	
Body mass index	Underweight/Normal	72	29.0	176	71.0	.611*	62	39.2	96	60.8	.419*	134	33.0	272	67.0	.333*
	Overweight/Obese	25	32.1	53	67.9		25	45.5	30	54.5		50	37.6	83	62.4	
Body perception	Underweight/normal	79	30.0	184	70.0	.819*	66	38.8	104	61.2	.233*	145	33.5	288	66.5	.520*
	Overweight/obese	18	28.6	45	71.4		21	48.8	22	51.2		39	36.8	67	63.2	
General health perception	Good	31	22.3	108	77.7	.005*	40	36.7	69	63.3	.026*	71	28.6	177	71.4	<.001*
	Moderate	43	31.2	95	68.8		28	37.8	46	62.2		71	33.5	141	66.5	
	Poor	23	46.9	26	53.1		19	63.3	11	36.7		42	53.2	37	46.8	

(*Continued*)

Table 4. Tobacco Use Status by Various Characteristics of the Research Group (*Continued*)

		First Grade					Fifth Grade					Total				
		Tobacco Use					Tobacco Use					Tobacco Use				
		Yes		No			Yes		No			Yes		No		
Variables (n = 539)		**n**	**%**	**n**	**%**	***P***	**n**	**%**	**n**	**%**	***P***	**n**	**%**	**n**	**%**	***P***
Presence of chronic disease	Yes	4	21.1	15	78.9	.393*	20	43.5	26	56.5	.682*	24	36.9	41	63.1	.613*
	No	93	30.3	214	69.7		67	40.1	100	59.9		160	33.8	314	66.2	
Habit of doing sports	Yes	53	38.1	86	61.9	.004*	39	44.3	49	55.7	.387*	92	40.5	135	59.5	.008*
	No	44	23.5	143	76.5		48	38.4	77	61.6		92	29.5	220	70.5	
Dealing with any branch of art	Yes	39	29.1	95	70.9	.830*	36	52.2	33	47.8	.020*	75	36.9	152	63.1	.285*
	No	58	30.2	134	69.8		51	35.4	93	64.6		109	32.4	203	67.6	
Friend's insistence on tobacco use	Yes	15	55.6	12	44.4	.002*	9	56.3	7	43.7	.192*	24	55.8	19	44.2	.002*
	No	82	27.4	217	72.6		78	39.6	119	50.4		160	32.3	336	67.7	
Communication with family	Good	66	26.4	184	73.6	.016*	71	40.8	103	59.2	.980*	137	32.3	287	67.7	.086*
	Moderate/poor	31	40.8	45	59.2		16	41.0	23	59.0		47	40.9	68	59.1	
Communication with friends	Good	69	28.4	174	71.6	.358*	65	38.0	106	62.0	.090*	134	32.4	280	67.6	.115*
	Moderate/Poor	28	33.7	55	66.3		22	52.4	20	47.6		50	40.0	75	60.0	
Mother tobacco use	Yes	26	38.2	42	61.8	.086*	24	51.1	23	48.9	.106*	50	43.5	65	56.5	.017*
	No	71	27.5	187	72.5		63	38.0	103	62.0		134	31.6	290	68.4	
Father tobacco use	Yes	45	39.5	69	60.5	.005*	34	42.0	47	58.0	.793*	79	40.5	116	59.5	.019*
	No	52	24.5	160	75.5		53	40.2	79	59.8		105	30.5	239	69.5	
Sibling tobacco use	Yes	29	44.6	36	55.4	.003*	30	48.4	32	51.6	.151*	59	46.5	68	53.5	.001*
	No	68	26.1	173	73.9		57	37.7	94	62.3		125	30.3	387	69.7	
Close friend tobacco use	Yes	96	37.8	62	62.2	<.001*	85	45.0	104	55.0	.001*	181	40.9	262	59.1	<.001*
	No	1	1.4	71	98.6		2	8.3	22	91.7		3	3.1	93	96.9	
Information about the harms of tobacco	Yes	95	30.0	222	70.0	>.05***	87	41.0	125	59.0	>.05***	182	34.4	347	65.6	.341***
	No	2	22.2	7	77.8		0	0.0	1	100.0		2	20.0	8	80.0	
Exposed to tobacco smoke	No	2	12.5	14	87.5	.163***	0	0.0	1	100.0	>.05***	2	11.8	15	88.2	.048*
	Yes	95	30.6	215	69.4		87	41.0	125	59.0		182	34.9	340	65.1	
Physicians should be an example	Yes	47	20.2	186	79.8	<.001*	43	28.9	106	71.1	<.001*	90	23.6	292	76.4	<.001*
	No	50	53.8	43	46.2		44	68.8	20	31.2		94	59.9	63	40.1	

*Chi-square.
**Fisher–Freeman–Halton (post hoc Bonferroni).
***Fisher's exact test.

Table 5. Factors Affecting Tobacco Use in the Research Group: Results of Logistic Regression Analysis

Variables (Affecting Factors/Reference Group)	First Grade		Fifth Grade		Total	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Gender (male/female)	1.31	0.70-2.47	-	-	1.50	0.99-2.28
Place of residence (With friend/others)	2.01	0.90-4.33	-	-	1.58	0.99-2.50
Communication with family (moderate or poor/good)	1.91	0.99-3.70	-	-	-	-
General health perception (moderate or poor/good)	1.84*	1.02-3.33	-	-	2.08**	1.38-3.15
Habit of doing sports (yes/no)	1.75	0.93-3.29	-	-	1.36	0.90-2.07
Insistence of friends on tobacco use (yes/no)	2.86*	1.19-6.88	-	-	2.08*	1.04-4.14
At least one of the family members using tobacco (yes/no)	2.39**	1.34-4.26	-	-	1.70*	1.14-6.43
At least one of the close friends using tobacco (yes/no)	29.72**	3.94-224.11	9.57**	2.10-43.58	14.49***	4.42-47.49
Physicians should set an example to society by not using tobacco (no/yes)	3.95***	2.19-7.14	4.95***	2.67-9.19	4.22***	2.77-6.43
Dealing any branches of art (yes/no)	-	-	0.60	0.33-1.08	-	-
Class (Fifth/First)	-	-	-	-	1.56*	1.01-2.40
Working status (working/not working)	-	-	-	-	0.95	0.41-2.22

For first grade model: Gender, place of residence, communication with family, general health perception, habit of doing sports, insistence of friends on tobacco use, at least one of the family members using tobacco, at least one of the close friends using tobacco, physicians should set an example to society by not using tobacco.
For fifth grade model: At least one of the close friends using tobacco, physicians should set an example to society by not using tobacco, dealing with any branches of art.
For total students model: Gender, place of residence, general health perception, habit of doing sports, insistence of friends on tobacco use, at least one of the family members using tobacco, at least one of the close friends using tobacco, physicians should set an example to society by not using tobacco, class, working status.
*$P < .05$.
**$P < .01$.
***$P < .001$.

that medical students are not sufficiently aware of their own position in terms of being an important role model in society in terms of health behaviors and having a critical impact on tobacco control. In a study in 3 medical faculties in Türkiye, it was shown that "for healthy life," "not interested in," and "religious affiliation" were the reasons for not smoking.[25] In this context, it is seen that the harm of tobacco to health is the most important deterrent for those who do not try it. In addition, the fact that the family/environment's reaction is the reason for not trying (especially for first grade) reveals the importance of creating an environment in which tobacco is not affirmed.

Many studies show that medical students start using tobacco before university education. Similarly, in this study, 59.4% of students start to use tobacco before faculty. In literature, the decrease in the tobacco trial age until the primary education years and the risk of starting to use tobacco indicate that interventions and advocacy activities on tobacco should be started from the initial years of the education process and that they should be continued before and during faculty. Similar to this study, in many studies with medical students, more than half of tobacco users want to quit. The high rate of students' willingness to quit is an indication that quitting activities to be implemented during faculty can be beneficial. In addition, the high rate of students trying to quit and their need/desire to receive support suggest that it is necessary to provide dropout counseling services for students.

In studies, it is seen that the presence of tobacco users among friends and in the social environment affects students' tobacco use. Similar to this study, in a study at Balıkesir University, it was found that friends' tobacco use increased students' tobacco use 6.2 times. A study in Myanmar found that students with close friends who smoke tobacco use 10.7 times more than those who do not.[10,27] It is thought that students start to use tobacco for reasons such as being included in social environments and being accepted by friends, and continue to use tobacco due to its strong addictive effect. In addition, the formation of close circles of friends from people of similar social status may also be related to this result (inverse causal relationship). In addition, the prevalence of tobacco use by assistant physicians and lecturers, who are role models for medical faculty students, and the difficulty of the educational process may explain the increase in the frequency of use despite progress in the medical faculty. In a study examining smoking addiction in doctors, it was seen that 42.1% of doctors smoked.[28] Although no significant relationship between income, scholarship, and parental education status and tobacco use in this study, it is known that social determinants of health (such as low income and education level) are an important

factor affecting tobacco use.[4] In this respect, the stress factor, which is one of the most common reasons for starting and continuing to use tobacco in disadvantaged groups, may come to the fore.

In this study, there was a significant relationship between the tobacco use of each family member and tobacco use of students, and the prevalence of tobacco use was 1.7 times higher in students whose family members smoked tobacco compared to those who did not smoke. According to a study in South Africa, the presence of a smoker in the household increases a student's smoking by 4.74 times.[29] It is thought that this situation is due to the interaction brought about by taking the elders as role models and sharing the same living environment. The absence of a relationship with the use of family members in fifth grade may be related to being away from the family for a long time. In the literature, there are studies that have a relationship between the tobacco use of family members and tobacco use of medical students, as well as studies that don't. In this study, it is seen that as general health perception improves, the prevalence of tobacco use decreases and moderate/poor general health perception increases tobacco use 2.1 times. In the literature, it is seen that as health perception deteriorates, the prevalence of tobacco use increases, and the reporting of poor health status in tobacco users increases significantly.[30] In this study, being exposed to a friend's insistence for tobacco use increased students' tobacco use 2.08 times. Similarly, in a study in South India, male medical students who were exposed to peer pressure were 21.91 times more likely to smoke compared to those who did not; in a study in Myanmar, tobacco use is 5.4 times higher among those who are exposed to peer pressure than those who do not.[27,31] Peer pressure is also an important reason to start using tobacco. Similar to this study in the literature, tobacco use is lower among medical students who think that physicians should set an example for society.[21,32] In this study, students who do not think that physicians should set an example for society by not using tobacco use 4.22 times more than those who do. In parallel with this finding, it is seen that students who do not use tobacco feel more responsible in this regard. These findings support each other.

The limitations of this study are that it is a cross-sectional design, it was conducted in a faculty, the sample selection method was not used, and the questioning of tobacco use as self-report.

It is seen that tobacco use is a common public health problem in medical students as well as in society and requires urgent intervention. Being studied in a higher class, having a moderate/poor general health perception, being exposed to the insistence of friends on tobacco use, at least one of their family members using tobacco, at least one of close friends using tobacco, and not thinking that physicians should be an example to society by not using tobacco are factors that increase the prevalence of tobacco use. Although the most common tobacco product is cigarette, the use of other products should not be ignored. In order to prevent the increase in tobacco use in higher classes, structured, systematic, and layered education should be given in accordance with the basic and clinical medical education periods from the beginning of faculty. Physicians should be supported with in-service training due to their position in tobacco control. Starting from primary–secondary education, tobacco should be included in the curriculum and it should be processed with methods that will provide skills to cope with stress. Counseling services should be provided in specialized units for young people, student's close environment should be included in interventions, educational environments should be made tobacco-free, and an environment in which tobacco is not positive should be created. Tobacco control measures should be fully implemented, necessary inspections should be carried out, and necessary sanctions should be applied in case of non-compliance. Young people should be included in advocacy activities and community participation should be ensured. Implementation of peer education models can be an effective intervention, as close friends and peers are important reasons for starting to use tobacco and are among the factors that increase the frequency of tobacco use. The reasons why medical school students start and continue using should be examined more deeply through qualitative research, and strategic interventions should be developed towards the cause. Initiatives aimed at social determinants of health (such as increasing scholarship opportunities) should not be ignored.

Ethics Committee Approval: This study was approved by the Ethics Committee of Dokuz Eylül University (approval number: 2022/35-10; date: 02.11.2022).

Informed Consent: Verbal and written informed consent was obtained from the students who agreed to take part in the study.

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Original Article

Smoking Cessation Support via Video Counseling (e-Cessation): A Promising Field for Telemedicine Implementation

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Abstract

OBJECTIVE: The study aimed to investigate the utility of telemedicine conducted via video counseling in comparison to the previous structured approach and to compare prepandemic smoking cessation success rates with traditional counseling.

MATERIAL AND METHODS: The applicants of the outpatient clinic for smoking cessation support pre- and post-pandemic periods were included in the study. The time intervals were retrospectively between 1 March and 30 August 2021 and the last 3 months of the year 2019. The data were revealed retrospectively. Age, sex, occupation, smoking history as package year, and the score of the Fagerström test for nicotine dependence, accompanying chronic diseases, treatment method, and quitting status between 6 and 9 months of follow-up.

RESULTS: The number of applicants was 200 (87% male) and 89 (95% male) in groups 1 and 2, respectively. The age difference was not significant. The difference was statistically significant according to having at least 1 accompanying chronic disease, specifically a lung disease. None of the parameters have affected the success of quitting smoking. The smoking cessation rate was 3.9 fold higher in the telemedicine group than in the traditional group.

CONCLUSION: The main principle appears to be allocating enough time, as required on an individual basis, to clearly assess the situation, including identifying barriers and options. Since immediate systematic physical examination and laboratory testing may not be mandatory for individuals seeking smoking cessation support, telemedicine emerges as a reasonable option and a promising field for comprehensive video counseling.

KEYWORDS: Smoking cessation, telemedicine, video counseling, video conference, remote health service

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INTRODUCTION

Since it was first announced as a pandemic by the World Health Organization (WHO) on 11 March, 2020,[1] a novel disease called coronavirus disease 2019 (COVID-19), caused by a new type of coronavirus type named SARS-CoV-2, has brought about numerous changes in daily life, both through compulsory measures and voluntary actions. These transformations have been particularly noticeable in the field of medicine due to the highly contagious nature of the disease, necessitating strict preventive measures such as the use of face masks, physical distancing, hygiene practices, limited social interaction, and travel restrictions. An example of this transition in healthcare services is the implementation of telemedicine. It has been introduced as an approach to "forward triage," which enables effective patient screening while simultaneously safeguarding patients, doctors, and the community from exposure to COVID-19.[2] Telemedicine has emerged as a solution to address the current challenges faced by healthcare systems worldwide during the pandemic, aiming to sustain the capacity to provide services not only for those affected by COVID-19 but also for individuals dealing with other acute and chronic diseases, while protecting physicians, nurses, and other allied health personnel.[3] While the implementation of this technological approach remains controversial in many countries, including Türkiye, it is still a global necessity to identify the areas suitable for telemedicine. Recently, a retrospective assessment of telemedicine via video conferences for COVID-19 patients has demonstrated its potential in forward triage, follow-up visits, and providing continuous remote healthcare support for these patients.[4] However, the medical interventions of telemedicine, whether they are suitable or not, await investigation through clinical studies. Smoking cessation support might be one such area due to its non-urgent nature, as it does not require immediate physical or radiological examinations.

In addition to numerous established risks that cigarette smoking poses to various organs of the human body, preliminary data suggest that it may also exacerbate the disease process in active smokers with COVID-19. A systematic literature review has hypothesized an association between smoking behavior and adverse COVID-19 progression, emphasizing the importance of quitting smoking.[5] Subsequently, a meta-analysis study revealed that smokers were

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nearly twice as likely to experience severe progression compared to non-smokers.[6] In fact, WHO published the Global Tobacco Control Report, which emphasized the promotion of comprehensive cessation interventions to aid in quitting tobacco use just prior to the COVID-19 Pandemic.[7] At the conclusion of that report, a global objective was articulated, stating "it is important that we all recommit to ensuring all the people of the world are protected fully from the great harms of the tobacco epidemic" (p. 6). On the other hand, smoking cigarettes or using other tobacco products is associated with the potential to increase the likelihood of virus transmission, primarily through the exhalation of respiratory droplets while exhaling tobacco smoke. The COVID-19 Pandemic has been addressed as an opportunity for tobacco use cessation.[8] While tobacco sales and smoking were banned in some countries, such as New Zealand, Portugal, and Mexico, those prohibitions may not achieve the desired results without increasing awareness of the associated risks and providing appropriate assistance for quitting smoking. While aiding smokers willing to quit and proactively igniting their motivation, it is crucial to ensure that COVID-19 prevention measures (such as the use of personal protective equipment (PPE) and practicing physical distancing) are properly adhered to. Incomplete measures would fundamentally result in inadequate protection. As mentioned by Kotsen and co-authors, the rapid transformation to maintain clinical care became an urgent necessity during the COVID-19 Pandemic, which saw a sudden disruption of routine healthcare services.[9] Smoking cessation support was among these services albeit not considered urgent.

It has been emphasized that limiting the utility of telemedicine limited to crisis periods would be a shortsighted view. It is necessary to draw the right conclusions from the lessons learned during the pandemic by a wide spectrum, including all parties from the telemedicine community to society at large.[3] Some of these lessons require evidence-based information derived from studies, as suggested by the WHO: "Digital options should ideally be compared with conventional approaches in large-scale well-designed studies. Researchers should analyze and interpret the results without prejudice of implied benefits of digitalization."[10]

Main Points

- This study highlights the feasibility of remote counseling, increasing awareness of telemedicine among physicians and patients.
- Clinical investigations are needed to assess the suitability of telemedicine for medical interventions, particularly in non-urgent cases such as smoking cessation support.
- We evaluated the effectiveness of smoking cessation support delivered via telemedicine and traditional methods in an outpatient clinic, with remote techniques showing significant advantages, especially during the pandemic.
- Incorporating technological methods into smoking cessation programs holds promise as an alternative approach.
- Additional research is required to gather more data on the effectiveness and broad applicability of telemedicine in smoking cessation support, as well as to address any potential drawbacks and technological solutions.

The aim of the recent study was to assess the effectiveness of telemedicine conducted via video counseling as an adaptation of the previous structured form. It aimed to compare the prepandemic results of the same team with face-to-face counseling conducted in physical presence in the same room. The study examined the feasibility of telemedicine for smoking cessation support by analyzing the success rate of quitting smoking in comparison to the traditional face-to-face method previously provided at the same healthcare facility.

MATERIAL AND METHODS

Background of Implementation of Telemedicine

Similar to other clinics in the country, all our outpatient clinics, including the smoking cessation outpatient clinic (SCOPC), were temporarily closed at the onset of the pandemic. The decision was made to prevent doctors and patients from potential COVID-19 contagion and to conserve healthcare resources during the crisis. However, one of the researchers initiated remote patient evaluation after the first three months of the pandemic. The technical system for this purpose was developed individually. When a patient scheduled an appointment through the university hospital's website, a video counseling session was arranged with the pulmonologist using a software program (Skype™, version 6.4, Microsoft, Redmond, WA, USA). Only patients who absolutely needed an in-person visit for either physical examination, testing, or prescription were invited to the hospital.[4] After gaining significant experience employing telemedicine for remote management of pulmonary diseases, the pulmonologist noticed the absence of the routine smoking cessation support provided in the prepandemic period. Considering the lower need for urgent physical examinations and laboratory tests, as well as the availability of relevant drugs free of charge from units designated by the Ministry of Health (MoH), the suitability of using telemedicine techniques for smoking cessation support was deemed reasonable. Consequently, the team began offering this support through telemedicine via video counseling at the SCOPC on March 1, 2021, making it the first center in the country to do so.

This study was carried out in accordance with the Helsinki Declaration and was approved by the Ethical Council of Pamukkale University (08.06.2021; E-60116787-020-61735). The data was retrieved retrospectively from the patient files, which included informed consent obtained routinely during the initial interviews. Written consent was obtained for the traditional group, while verbal consent was obtained for the telemedicine group.

Features of the Telemedicine and Traditional Groups

The study included applicants of the SCOPC during both the pre- and post-pandemic periods. Group 1 consisted of applicants who received real-time video counseling via telemedicine between March 1 and August 30, 2021. Group 2 was designed as a historical control group with the applicants of the traditional SCOPC. Inclusion for this group was limited to the last three months due to interrupted service caused by a lack of drug supply from the MoH before and after this duration in the prepandemic period. Data for these applicants

were retrospectively revealed from their health records, and the latest information on their smoking status was obtained through telephone calls. The same parameters in group 1 were also retrospectively retrieved from the health records of applicants in group 2 to facilitate comparison.

The independent variables included age, sex, occupation, smoking history quantified as package-years, and the Fagerström Test for Nicotine Dependence score. The accompanying chronic diseases for each group were listed in decreasing order. Information regarding psychosocial and pharmacological treatment, including the use of varenicline or nicotine replacement therapy (NRT), was obtained from the patient's health records.

All study applicants were followed for a minimum of 6 months, ranging from 6 to 9 months, following their initial consultation with the doctor. In group 1, follow-up appointments were conducted via telemedicine. Information regarding smoking cessation status and any challenges encountered during the quitting process within the 6-to-9-month period was also collected. The duration of video counseling was recorded for the initial and each subsequent meeting. However, the duration of visits in group 2 could not be retrieved retrospectively as this data was not documented during in-person appointments.

The management for the applicants in group 1 and group 2 involved providing the relevant treatment for a minimum of 3 months. In the event of premature discontinuation of the treatment due to the applicant's preference, a close follow-up was scheduled, and immediate support for the potential cravings to smoke was offered. Treatment success was defined as abstaining from smoking for a minimum of 6 months, given the variation in follow-up duration ranging from 6 to 9 months in group 1.

Sample size was calculated using Riskcalc sample size calculator based on previous research findings. It was assumed that the smoking cessation success would be 80% at both treatment arms, and the threshold amount for the non-inferiority test should be 15%. At the 5% level of significance, with 2:1 allocation and a 10% drop rate, the minimum sample size calculated for the control arm was 66, and for the telemedicine group, n=198 achieved an 80% power for the analysis.

Out of the total 89 applicants in group 2 contacted by telephone for this study, smokers who expressed a strong desire to quit smoking were informed about the telemedicine option for smoking cessation support and were invited to consider it. Appointments were scheduled for those who requested assistance beyond the scope of the study.

For both groups, individuals lost to follow-up were contacted via telephone calls to obtain the relevant information. If deemed necessary for further follow-up visits, the next meeting was scheduled during these phone calls to maintain continuity. Applicants who did not request a follow-up visit, did

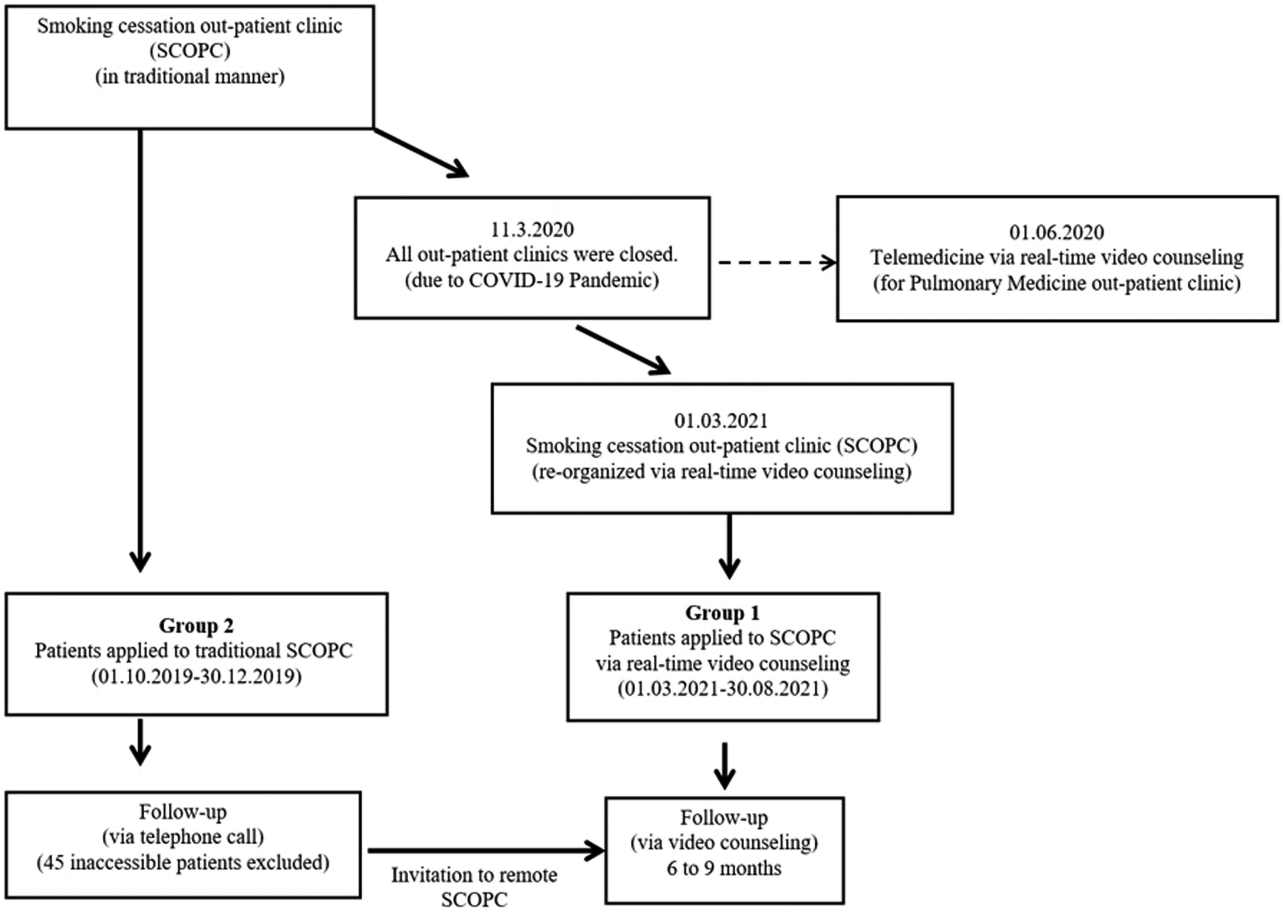


Figure 1. Time frame of the study design based on smoking cessation out-patient clinics with traditional in-person and telemedicine methods.

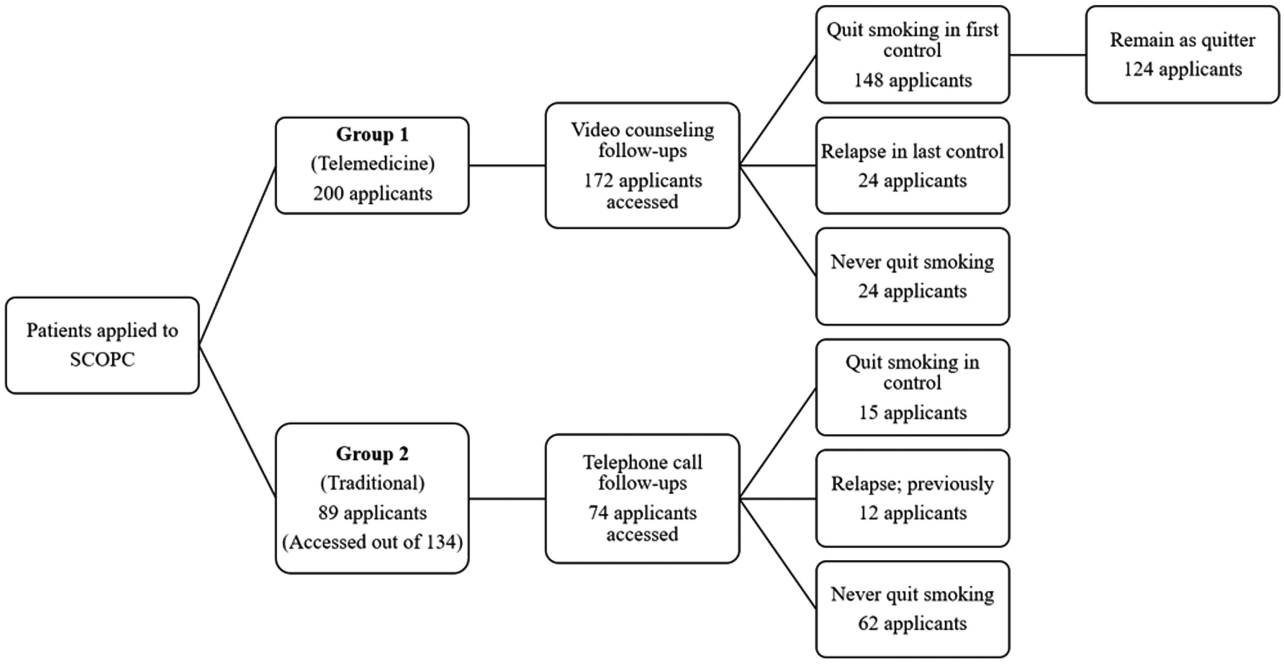


Figure 2. Flowchart of study groups in relation to type of counseling and the outcomes of smoking cessation support. SCOPC, Smoking Cessation Out-Patient Clinic.

not respond to telephone calls, or had inaccurate telephone numbers were also included in the study, and their apply for a follow-up visit, who didn't answer the telephone call or whose telephone number was declared inaccurate was also included to the study, and their status was noted.

The study design timeline and the formation flowchart of the groups have been summarized in Figure 1 and Figure 2, respectively.

Statistical Analysis

In descriptive statistics, continuous variables are presented as mean ± SD. Categorical variables are presented with their percentages. Between group comparisons for continuous data were made by *t*-test or non-parametric equivalent Mann–Whitney *U*-test. Categorical data were compared with chi-square test. Normality of the distribution was assessed with Kolmogorov–Smirnov test. A multivariate logistic regression model was applied to investigate the relationship between independent variables and smoking cessation success. Odds ratios obtained from logistic regression are presented with their 95% CI. The statistical analyses were performed by the Statistical Package for Social Sciences (SPSS®) software, version 20 (IBM Corp.; Armonk, NY, USA). A two-sided $P < .05$ is considered statistically significant.

RESULTS

Demographic Features

In group 1, data from 200 applicants were analyzed. The group was predominantly composed of male smokers, accounting for 87% (174 smokers), while the remaining 13% (26 smokers) were female. In group 2, a total of 89 applicants were included in the analysis. However, out of 134 registered in 2019, due to a falsely declared telephone number, 15 of them could not be reached, and at least three consecutive telephone calls were inconclusive for the remaining 30 applicants. In group 2, 95% of the total 89 smokers were male (85 smokers). There was a statistically significant difference in the female/male ratio between the two groups ($P = .029$). The groups were compared according to age, smoking history, and nicotine dependency level. The mean age was higher in group 1 while the differences were not statistically significant for other parameters (Table 1).

There was no accompanying chronic disease in 157 applicants of group 1 (78.5%). The distribution of the diseases in the remaining applicants was presented in decreasing order: chronic obstructive pulmonary disease (COPD) in 19, coronary arterial diseases in 16, diabetes mellitus in 14, arterial hypertension in 12, lung cancer in 12, asthma in 7, mitral

Table 1. Mean Values of Age, Smoking History, and Nicotine Dependency Scores According to the Groups

Parameter	Group 1 (n = 200)	Group 2 (n = 89)	*P*
Age (mean ± SD) (range)	40.15 ± 13.41 (18-69)	35.62 ± 10.21 (18-64)	.002*
Smoking history as pack-years (mean ± SD) (range)	29.9 ± 24.27 (1-150)	27.21 ± 23.81 (5-130)	.381**
Nicotine dependency score (mean ± SD) (range)	6.34 ± 2.54 (0-10)	6.58 ± 2.30 (2-10)	.439**

Values with $P < .05$ are significant.
*t-test.
**Mann–Whitney *U* test.

Table 2. Mean Durations of the First Counseling and Follow-up Meeting According to the Groups

Parameter	Group 1 (n = 200)	Group 2 (n = 134)	*P*
Duration of first counseling as minutes (mean ± SD); (range)	20 ± 3.83 (15-35)	NA	-
Duration of follow-up meeting as minute (mean ± SD); (range)	10 ± 3.5 (5-20)*	5.3 ± 1.3 (5-10)**	<.001***

Values with $P < .05$ are significant.
NA, not applicable.
*Via video counseling.
**Via telephone call.
***Mann–Whitney *U*-test.

valve disease in 3, obstructive sleep apnea in 3, larynx cancer in 3, breast cancer in 1 of them. In group 2, there were no accompanying chronic diseases in 81 of the applicants (91%). The distribution of the diseases in the remaining applicants was presented in decreasing order: diabetes mellitus in 4, arterial hypertension in 4, coronary arterial diseases in 3, COPD in 1, diffuse interstitial lung disease in 1 of them. The difference was statistically significant between group 1 and group 2 according to having at least one accompanying chronic disease (21.5% vs. 9%, $P = .01$). Additionally, in comparison for having a lung disease, the difference was significant between group 1 and group 2 (17% vs. 4.5%, $P = .004$).

Characteristics of Treatment Interventions

Time Spent on Counseling in Telemedicine vs. Traditional Smoking Cessation Outpatient Clinic

The duration of each video counseling (for first and follow-up meetings) was recorded using the Skype program in the telemedicine group. However, this parameter was not applicable for traditional in-person first meetings in the doctor's office before the pandemic period (group 2). The data are summarized in Table 2.

Treatment Choices

In group 1, the treatment choices consisted of varenicline in 190 applicants and NRT for 10 applicants out of a total 200 applicants. None of the applicants in group 1 were followed without pharmacological treatment. In group 2, the uptake rates for varenicline and NRT were 52 (58.4%) and 33 (37.1%), respectively, among the 89 applicants who could be reached for follow-up visit via telephone call. The remaining 4 (4.5%) applicants in group 2 received no pharmacological treatment in 2019.

Outcomes Related to Smoking Cessation Support Success

In group 1, follow-up visits were conducted with 172 out of the total 200 applicants who had agreed to a smoking cessation plan. The remaining 18 applicants were contacted at least three times using the telephone numbers they provided at the registration to the SCOPC but could not be reached (5 of them were found to have provided false numbers). At the first follow-up visit, 124 of the applicants (62%) had successfully quit smoking. Considering the 6-9-month follow-up period, 24 applicants (13.9%) resumed smoking after 1-3 months. After excluding these 24 applicants who had failed to quit smoking for at least 6 months, the treatment success rate has reached 88 (44%) out of the total 200 applicants. Theoretically, there would be two extreme scenarios for treatment success if inaccessible 18 applicants could be included in the cohort: 106 (%53) when all 18 were quitters, 44% when all 18 had failed to quit smoking, and the other possibilities were between these two percentages.

The reasons for the failure to quit smoking were also recorded in the routine questioning of relevant applicants. The main issues, except the high desire of smoking due to a high level of nicotine dependency, were listed as periodical traumatic stress factors that interrupted the process, such as experiencing COVID-19, having a family member diagnosed with or died from COVID-19, and encountering unexpected work-related problems.

Table 3. Multivariate Logistic Regression Analysis of Smoking Cessation Success and Independent Variables

Independent Variables	Model 1	Model 2
	Odds ratio (95% CI)*	Odds ratio (95% CI)*
Age	1.001 (0.974-1.029)	1.002 (0.975-1.030)
Gender (female) Reference: male	0.881 (0.388-1.998)	0.899 (0.395-2.046)
Chronic diseases: yes Reference: no	0.865 (0.420-1.782)	0.859 (0.416-1.772)
Nicotine dependency (Fagerström)	0.932 (0.840-1.035)	0.930 (0.838-1.033)
Smoking history (pack-years)	1.000 (0.986-1.015)	1.000 (0.986-1.015)
Telemedicine group Reference: routine care	3.925 (2.073-7.435)	3.753 (1.938-7.266)
Duration of follow-up meeting	–	1.022 (0.940-1.112)

*Multivariate logistic regression analysis.

In group 2, the success rate of smoking cessation support was found to be 16.9% (15 patients) as they successfully quit cigarette smoking and remain quitters. However, 12 applicants (13.4%) who initially quit smoking later relapsed, and 62 applicants (69.7%) were unable to quit smoking.

Comparing the rate of applicants who successfully quit smoking in group 1 and group 2 (88 or 44% vs. 15 or 16.9%, respectively), the efficacy of telemedicine intervention for smoking cessation support was significantly higher than that of in-person intervention ($P < .001$). Furthermore, in the follow-up assessments, the rate of quitters who relapsed and started smoking again after at least 1-3 months of being smoke-free was similar between the two groups with 24 applicants (12%) in group 1 and 12 applicants (13.5%) in group 2.

Although there was a statistically significant difference in age, gender, and the presence of accompanying disease between the two groups, these parameters did not show a significant effect on the treatment success rate in the logistic regression analyses. Additionally, neither the presence of accompanying chronic diseases nor the presence of the lung disease, nor the number of accompanying chronic diseases had a significant effect on the treatment success rate for smoking cessation. Taking all the confounding parameters into consideration in the statistical analyses, the smoking cessation rate in the telemedicine group (group 1) was 3.9 times higher than that in the traditional in-person group (group 2) (95% CI, 2.073-7.435) (Table 3). When we take into account the duration of the follow-up meeting as a possible confounder in model 2, it had no significant impact on the results.

DISCUSSION

The effectiveness of smoking cessation support provided in the same outpatient clinic, both before and during the pandemic periods, using the traditional method or via telemedicine was evaluated. The data revealed a notable advantage for the remote technique, particularly in the context of the pandemic. Discussing this result in relation to the procedure beyond the pandemic conditions could provide valuable insights for future implementations in ordinary circumstances.

A study aimed to evaluate Internet-based video counseling for smoking cessation support, conducted just before the pandemic with the goal of eliminating one of the key obstacles—face-to-face clinic visits—revealed noninferiority based on the similar efficacy results.[11] However, due to the lack of data obtained in comparison with no intervention control or any behavioral smoking cessation intervention other than telephone counseling (e.g., face-to-face), Tzelepis et al[12] concluded in their Cochrane analysis that well-structured studies were needed to determine whether real-time video counseling increases smoking cessation rates. While telemedicine has been suggested for post-pandemic use due to its advantages, such as supporting the healthcare system, improving patient-physician communication even under protective measures, and reaching more patients,[13] its utility in different fields, including giving smoking cessation support, should be investigated. Therefore, the results of the recent study may offer valuable insight into this matter.

Just before the pandemic, WHO released multidimensional guidance for digital health with the aim of inspiring and influencing future research efforts in digital applications.[10] These interventions can encompass various fields, including utilizing new technology to provide evidence-based information and resources to tobacco users (e.g., applications, mobile phones, Quitlines, social media), delivering brief cessation advice in healthcare settings, offering telehealth services or applications for users seeking cessation advice, enhancing access to free or low-cost pharmacotherapy (e.g., cessation medications and nicotine replacement therapies), and providing behavioral counseling.[8] A study on the Youth Quitline service and the quitting behaviors of its users in Hong Kong reported increases in the number of incoming calls and quit rate among the participants during the COVID-19 pandemic. Among participants, 43% mentioned the pandemic's effect on their motivation to quit, and 83% changed their smoking habit during the pandemic.[14] Cumulative data support the value of video counseling as a telemedicine approach, and other devices are also under recent evaluation. Based on their findings, Haluza and colleagues have suggested adding the use of mobile applications (Apps) as the sixth "A" to the standard 5A strategy (Ask, Advice, Assess, Assist, and Arrange).[15] There appears to be potential in incorporating technological methods as an option to smoking cessation programs.

The prevalence of smoking tends to increase from adolescence into young adulthood. Fortunately, young adult smokers often express interest in smoking cessation and are more likely to make quit attempts compared to older adults.[16] However, successful cessation in middle-aged and older adult groups has been associated with factors like willpower and comorbidities.[17] In a recent study, it was observed that applicants who received smoking cessation support before the pandemic through traditional in-person face-to-face methods were generally younger than those in the telemedicine group. It's important to note that technology may not pose a barrier to accessing healthcare services, as both groups included participants ranging in age from 18 to their 60s. Furthermore, there was no significant difference in success rates for quitting smoking based on age.

A meta-analysis of studies published in Latin America on quitting cigarette smoking through mobile health interventions has underscored the need for further randomized controlled studies, despite the promising results.[18] In the recent study, data for the control group were retrospectively obtained from the records of individuals who applied in-person for smoking cessation support to the same outpatient clinic during the prepandemic period. Synchronized randomization into the control and telemedicine groups was not feasible due to the necessity of implementing telemedicine as video counseling during the pandemic, when the traditional method had to be interrupted, as was the case in similar facilities. If telemedicine had not been voluntarily implemented in the pulmonary outpatient clinic,[4] it would not have been possible to continue smoking cessation support. Under these circumstances, the comparison can be considered acceptable, given that the traditional control group provided data from the smoking cessation support given during the prepandemic period by the same team and structured process. Furthermore,

the similarities in gender, smoking history, and nicotine dependency scores between the telemedicine and control groups allow for a reasonable comparison. Although the presence of accompanying chronic disease (either general or pulmonary) in the control group was much lower than in the telemedicine group, it had no impact on the treatment success rate.

In our hospital, there is only one outpatient clinic within the pulmonary medicine department, and smoking cessation support is provided by pulmonologists. Since the implementation of telemedicine via video conferencing for general pulmonary diseases began in this department at the onset of the COVID-19 pandemic, the experience gained from routine use was subsequently applied to smoking cessation support. By considering the results of the patient perspective study conducted on the general patient population regarding telemedicine, pulmonologists employed the same method to provide smoking cessation support to applicants. The advantages of this model for telemedicine, by the patients, include avoiding travel and long waits at the hospital, saving time and energy, receiving comfortable counseling with a physician about their health issues, and being invited by the physician only when necessary. Time has two aspects, one involving using time efficiently by avoiding unnecessary hospital visits and waiting in line for examination or evaluation of tests ordered by the physician, while the other aspect involves allocating sufficient time as needed for each applicant.[19] Anastasi et al[20] reported that no parameter influenced the quit rate except for the proportion of time spent delivering smoking cessation support. While there may be many confounding factors influencing the success of smoking cessation support, the primary principle appears to be allocating enough time, tailored to the individual's needs, to clearly identify the barriers and available options. During a pandemic, physical presence together can be challenging due to preventive measures and the discomfort caused by communication while wearing PPE. In the recent study, the mean duration of the first real-time video counseling session was 20 minutes. This duration is significantly longer than what would have been feasible for in-person sessions during pandemic circumstances.

The follow-up visits to assess the success of the traditional face-to-face method were conducted by telephone calls in the recent study. The sole objective of these calls was to retrospectively evaluate the quit rate in the traditional group. The mean duration of these calls was approximately half of the duration of the follow-up visits in the telemedicine group. In terms of using telephone calls, the recent study highlights a significant finding, revealing challenges in reaching participants due to incorrect telephone numbers provided by the participants themselves and a lack of response to repeated calls. However, using telephone calls might serve as a viable method throughout the whole process. Nevertheless, the data was inconclusive regarding whether telemedicine was superior to counseling for cessation support via telephone. Richter and colleagues reported a higher rate of prescription drug usage for cessation support in the telemedicine group and suggested this method for relatives and friends.[21] Another study that evaluated the impact of adding telephone-based smoking cessation counseling, incorporating lung cancer screening, did not show an increase in 12-month cessation rates compared to providing written information.[22] While acknowledging methodological limitations, Tzelepis et al[12] found no difference between real-time video counseling and telephone counseling for smoking cessation.

Recent findings from a meta-analysis of studies in Latin America have shown promising results for technology-based smoking cessation interventions, including telemedicine and mobile health services. The need for additional support through long-term studies has been emphasized.[18] In a randomized controlled study that assessed the impact of incorporating telemedicine into mobile interventions supporting psychopharmacological treatments, telemedicine demonstrated a greater contribution to achieving a 1-year cessation rate compared to psychopharmacological treatment alone.[23] Tobacco addiction treatment was administered using either Varenicline or NRT, depending on the available treatments, both the traditional in-person and telemedicine methods. Pharmacological treatment was typically prescribed following structured counseling, whether through telemedicine or in-person. It is not possible to conclude that telemedicine favored one method over the other, as the choice of medication was primarily based on the available drug options provided by MoH during the respective periods.

At the onset of the COVID-19 pandemic, smoking cessation support was immediately suspended due to the urgent need to combat a novel, highly contagious, and potentially fatal infection. On the other hand, subsequently, the importance of quitting smoking has been shown in relation to the higher severity of COVID-19 in smokers and the increased risk of contagion from smoking, and the necessity of continuing smoking cessation support has been highlighted.[24] Since the high risk of contagion was the main concern about giving this support face-to-face at traditional in-person circumstances, telemedicine emerged as one of the alternatives that allows both remote and interactive counseling without time constraints. The acceptance of this technological novel approach requires favorable data from relevant studies. The results of a study on using telemedicine for smoking cessation support in cancer patients at the onset of the COVID-19 pandemic revealed a higher ratio of attendance to the appointment and acceptable effectiveness of telemedicine.[9] The protocols for appointments and video counseling in the recent study were similar to those in this study. In a recent study, using video counseling for smoking cessation support was found to be effective and non-inferior to the traditional in-person method. Furthermore, the success rate in quitting smoking was 3.9 times higher in the telemedicine group compared to the traditional in-person method.

In a randomized controlled multicenter study conducted before the COVID-19 pandemic, Nomura and colleagues compared the effectiveness of two methods: telemedicine via video counseling and standard face-to-face counseling for cigarette cessation support. They found that the two groups were similar in terms of initial nicotine dependency scores and withdrawal symptoms at the 9th and 12th weeks. Telemedicine was shown to be non-inferior to the traditional face-to-face counseling in terms of success in cessation rates.[11]

In the recent study, the ratio of applicants who quit cigarette smoking was higher in the telemedicine group, and the telemedicine technique was not inferior to the traditional standard face-to-face group as long-term relapse rates were similar.

An important result of the recent study was the reasons for the failure to quit of smoking. Although the most frequent reason was a high desire to smoke related to a high level of nicotine dependency, as expected, other reasons included stress factors such as receiving a COVID-19 diagnosis, either for oneself or a family member, and the loss of a relative due to COVID-19. These findings underscore the importance of further studying pandemic-specific psychological support that can be provided through telemedicine. This data might also prove useful in dealing with extraordinary conditions that affect many people in the future.

There are some limitations to be mentioned in the recent study. Firstly, the study was conducted in one smoking cessation clinic, which might limit the generalizability of the findings. Second, there might be some unobserved variability due to unmeasured variables, such as income. Thirdly, the baseline characteristics of the intervention and control groups differed in terms of age and gender; however, we took into account the possible confounding effect of these variables by using multivariable logistic regression in the statistical analysis.

Although there may be many confounding factors related to the success of smoking cessation support, the main principle appears to involve sparing enough time, which may be defined as necessary on an individual basis, to clearly identify the situation consisting of barriers and options. During a pandemic, it is almost unfeasible to be physically present together for extended durations due to preventive measures. Nevertheless, discomfort can arise from communication under PPE. Additionally, using remote methods after the pandemic period can be an effective option for the smokers eager to quit living far from the healthcare units or being incapable of traveling there for initial evaluation and control visits. Since immediate systematic physical examination and laboratory testing might not be obligatory for individuals seeking smoking cessation support, telemedicine appears to be a reasonable option for comprehensive video counseling in this healthcare service. However, further studies are needed to collect more data on the effectiveness and widespread applicability of telemedicine, as well as to address any disadvantages and their solutions in instructing technological approaches to smoking cessation support.

Since telemedicine is a novel healthcare method, it is important to discuss relevant terminology, and the acceptance or rejection of these terms should be based on *profit and loss* evaluations, considering social aspects as well. From this perspective, suggested terms for smoking cessation support provided through telemedicine could be “tele-cessation” or “e-cessation.” While the latter may evoke associations with a harmful tobacco product (e-cigarette), it can also represent both a technological approach and the need for cessation from other tobacco products as well.

Ethics Committee Approval: This study was approved by the Ethics Committee of Pamukkale University (approval number: E-60116787-020-61735; date: 08.06.2021).

Informed Consent: The data was retrieved retrospectively from the patient files, which included informed consent obtained routinely during the initial interviews. Written consent was obtained for the traditional group, while verbal consent was obtained for the telemedicine group.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.A.; Design – G.A., M.M.; Supervision – G.A.; Resources – M.M., S.K.; Materials – M.M., S.K.; Data Collection and/or Processing – G.A., M.M., S.K., K.O.; Analysis and/or Interpretation – K.O., G.A.; Literature Search – G.A., M.M.; Writing – G.A., M.M., S.K.; Critical Review – K.O.

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Original Article

Latent Tuberculosis Infection Management in Solid Organ Transplantation Recipients: A National Snapshot

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Abstract

OBJECTIVE: Latent tuberculosis infection (LTBI) screening is strongly recommended in the pre-transplant evaluation of solid organ transplant (SOT) recipients, although it remains inadequate in many transplant centers. We decided to investigate pre-transplant TB risk assessment, LTBI treatment, and registry rates in Türkiye.

MATERIAL AND METHODS: Adult SOT recipients who underwent tuberculin skin test (TST) and/or interferon-gamma release test (IGRA) from 14 centers between 2015 and 2019 were included in the study. An induration of ≥5 mm on TST and/or probable/positive IGRA (QuantiFERON-TB) was considered positive for LTBI. Demographic features, LTBI screening and treatment, and pre-/post-transplant TB history were recorded from the electronic database of transplantation units across the country and pooled at a single center for a unified database.

RESULTS: TST and/or IGRA were performed in 766 (33.8%) of 2266 screened patients most of whom were kidney transplant recipients (n = 485, 63.4%). LTBI screening test was positive in 359 (46.9%) patients, and isoniazid was given to 203 (56.5%) patients. Of the patients treated for LTBI, 112 (55.2%) were registered in the national registry, and 82 (73.2%) completed the treatment. Tuberculosis developed in 6 (1.06%) of 563 patients who were not offered LTBI treatment.

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CONCLUSION: We determined that overall, only one-third of SOT recipients in our country were evaluated in terms of TB risk, only 1 of the 2 SOT recipients with LTBI received treatment, and half were registered. Therefore, we want to emphasize the critical importance of pretransplant TB risk stratification and registration, guided by revised national guidelines.

KEYWORDS: Solid organ transplantation, tuberculosis, latent tuberculosis infection, interferon-gamma release test, tuberculin skin test
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INTRODUCTION

Tuberculosis (TB) is still one of the world's most predominant infectious causes of morbidity and mortality since the 18th century when TB became epidemic in Western Europe.[1] According to the World Health Organization data, 20 million people developed TB and 1.5 million people died from TB in 2020, thus TB has become the second leading cause of infectious killer after COVID-19.[2]

Tuberculosis risk is increased in immunosuppressive conditions. Solid organ transplant (SOT) recipients have a 20-74 times increased risk of active TB.[3,4] The pooled prevalence of post-transplant active TB was estimated at 3%[5] and in cohort studies the overall median incidence has been reported as 2.37% (0.05%-13.27%) with higher incidences in endemic regions.[6] Tuberculosis incidence has been reported 15/100 000 for Türkiye in 2020[7] and TB prevalence in SOT was found to be 3.2% in a recent meta-analysis conducted in 4553 Turkish SOT recipients.[8] Since TB-related morbidity and mortality in SOT recipients are high, prevention and early recognition of TB infection is critical. There have been TB consensus guidelines for a long time; however, the diagnosis and management of LTBI have not been mentioned in a separate section detailed with brief recommendations.[9,10]

SOTprocedure, started in 1975 in Türkiye; however, routine pretransplant TB risk screening protocol has been established recently, therefore we aimed to investigate the practice in latent TB infection (LTBI) screening in SOT recipients and donors as well as posttransplant follow-up, registry rates, and TB prevalence in a given period in Türkiye.

MATERIAL AND METHODS

We conducted a retrospective descriptive study including 14 centers (36 clinics) from different regions of Türkiye and reviewed the data of all registered adult (age >18 years/old) SOT recipients. Patients who had undergone pretransplant LTBI screening with tuberculin skin test (TST) and/or interferon-gamma releasing assay (IGRA) between January 2015 and December 2018 were included in the study. The study was approved by the Ethics Cmmittee of Dokuz Eylül University (September 4, 2014, 2014/28-13). An informed consent form is not required due to the fact that it is a retrospective study.

Demographic characteristics and TB risk factors, pre/post-t ransplantation TB history, and LTBI screening procedure were recorded from the electronic database of each transplantation unit and combined for a nationwide united database. The findings were also checked with the national registry of the national "Ministry of Health, General Directorate of Public Health, and Department of Tuberculosis."

Latent Tuberculosis Infection Diagnosis

Tuberculin Skin Test

Tuberculin skin test was performed in standard procedure and interpreted 48/72 hours after the administration.

Interferon Gamma Releasing Assay

Interferon-gamma releasing assay was performed in registered laboratories nationwide with a commercial kit approved by the Ministry of Health.

An induration of ≥5 mm on TST and/or probable and positive IGRA (QuantiFERON TB) was considered positive for LTBI.

Diagnosis of Tuberculosis

Solid organ transplant recipients with posttransplant TB were identified, and posttransplant TB prevalence was calculated. Patients with symptoms, signs, and radiological findings (cavities, consolidation, bronchopneumonia, lymphadenopathy) suggestive of active TB infection whose microbiological specimens were positive for acid-fast bacilli and/or have a histopathological diagnosis of caseating granuloma were considered to have TB.

Latent Tuberculosis Infection Indications and Treatment Protocols

Either an induration of ≥5 mm on TST and/or probable and positive IGRA (QuantiFERON TB) was considered positive for LTBI. A standard LTBI treatment protocol with isoniazid given daily for 9 months was considered unless SOT recipients have received a prior adequate course of LTBI or active TB treatment.

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences version 24.0 (IBM Corp., Armonk, NY, USA). Data were expressed as mean and standard deviation or median and minimum–maximum values according to the distribution of the data. Nonparametric variables were compared by Mann–Whitney *U*-test, and categorical data were evaluated by chi-square or Fisher's exact test. A *P*-value of <.05 was considered significant.

Main Points

- Pretransplant tuberculosis (TB) screening is important to avoid post-transplant TB infection-related morbidity and mortality in solid organ transplant (SOT) recipients.
- There are efficient laboratory tests for determining latent tuberculosis infection (LTBI).
- Although guidelines recommend screening and treatment of LTBI, compliance rates to recommendations are not as desired depending on the pretransplant procedures of the transplantation center and transplanted organs.
- Latent tuberculosis infection screening and treatment in SOT recipients should be re-evaluated by national guidelines and tracked by registration.

Results

For the given period, 2266 SOT recipients from 14 centers and 2 participants from the Ministry of Health were included. Tuberculin skin test and/or IGRA were administered to 766 (33.8%) of them (Figure 1). The pretransplant LTBI screening rate ranged between 2.2% and 100% depending on the transplantation center. Within these 766 patients, most of them were kidney transplant recipients (n = 485, 63.4%). Males were predominant and mean ages ranged from 35.6 to 51.0 according to donated organs (P = .023) (Table 1). Among the factors associated with the likelihood of active TB risk, prior contact with an active TB patient was observed in 23 (3.0%), while fibrotic lesions compatible with LTBI were found in 84 (10.9%). Demographic and clinical features of the patients according to donated organs are shown in Table 1.

The pretransplant LTBI screening test positivity rate was 46.9% (minimum 31.1%–maximum 83.3%), and TST was the most preferred method for screening. Latent tuberculosis infection screening tests were most frequently applied in heart transplantation recipients (83.3%), although none were offered treatment (Table 2).

Isoniazid (INH) was the treatment choice for LTBI treatment and was given to more than half of the screened patients (60.8%). Half of them (n = 104, 51.2%) started treatment on the post-transplant first day. National registry notification for LTBI treatment was only performed for half of the patients (n = 112, 55.2%). Most of the patients to whom LTBI was offered completed the treatment (n = 82, 73.2%) (Table 3).

Among the study population, posttransplant TB was observed in 6 (1.06%) patients, 3 of these patients had risk factors for TB, and only two had LTBI screening but had not received LTBI treatment despite being positive.

DISCUSSION

The risk of TB infection as well as TB-related and SOT-related morbidity is increased in SOT recipients. There are existing guidelines for pretransplant screening in SOT recipients to reduce the risk of TB disease in SOT recipients and LTBI screening and treatment is recommended for transplant candidates and recipients considered at high risk of TB.[11-13] In Türkiye, a section for SOT recipients has recently been added to the national "Tuberculosis Diagnosis and Treatment Directory." Therefore, we aimed to investigate the practice for LTBI screening and treatment in SOT recipients and candidates across Türkiye.[14]

We evaluated 766 patients among 2666 SOT recipients to whom TST and/or IGRA were administered, representing one-third of the SOT recipients. Most of them were kidney

Table 1. Demographic and Clinical Features of the Study Population According to Donated Organ

Characteristics n (%)	Kidney (n = 485)	Liver (n = 206)	Lung (n = 45)	Heart (n = 30)	Total (n = 766)
Age (mean ± SD)	40.9 ± 13.1	51.0 ± 13.2	47.4 ± 12.1	35.6 ± 9.0	43.8 ± 13.7
Gender (male)	317 (65.4)	141 (68.4)	38 (84.4)	26 (86.7)	522 (68.1)
Donor source (living)	363 (74.8)	130 (63.1)	-	-	493 (64.4)
Prior tuberculosis exposure	11 (2.3)	8 (3.9)	4 (8.9)	-	23 (3.0)
LTBI radiological evidence	15 (3.1)	24 (11.7)	45 (100)	-	84 (10.9)

LTBI, latent tuberculosis infection.

Table 2. Latent Tuberculosis Infection Screening Test Application and Positivity Rates According to Donated Organ

	Positive Test/Applied Test				
LTBI Screening Test n (%)	Kidney (n = 485)	Liver (n = 206)	Lung (n = 45)	Heart (n = 30)	Total (n = 766)
TST	181/400 (45.3)	103/147 (70.1)	-	24/29 (82.7)	308/576 (53.9)
QuantiFERON-TB	12/55 (21.8)	8/17 (47.1)	14/45 (31.1)	-	34/117 (29.0)
TST and QuantiFERON-TB	7/30 (23.3)	9/42 (21.4)	-	1/1 (100)	17/73 (23.3)
Total	200/485 (41.2)	120/206 (58.3)	14/45 (31.1)	25/30 (83.3)	359/766 (46.9)

LTBI, latent tuberculosis infection; SOT, solid organ transplantation; TB, tuberculosis; TST, tuberculin skin test.

Table 3. Latent Tuberculosis Infection Treatment Offer, Registration, and Completion Rates According to the Donated Organs

LTBI Treatment	Kidney (n = 485)	Liver (n = 206)	Lung (n = 45)	Heart (n = 30)	Total (n = 766)
Recommendation	159/200 (79.5)	36/120 (30.0)	8/14 (57.1)	-	203/334 (60.8)
Notification to national registry	94/159 (59.1)	12/36 (33.3)	6/8 (75.0)	-	112/203 (55.2)
Completion	70/159 (44.0)	7/36 (19.4)	5/8 (62.5)	-	82/203 (40.4)

LTBI, latent tuberculosis infection.

transplant recipients due to more kidney transplantations than others. Males were predominant and the mean age was 43.8 ± 13.7, heart and kidney transplant recipients were the youngest. In a review that evaluated a total of 187 studies from 1998 to 2016, 2082 cases of TB after SOT have been identified. The median age was 45, males, and kidney transplantations were predominant.[6] In another systematic review and meta-analysis examined the pooled prevalence of active TB after transplantation, no difference between the mean/median age of transplant recipients across the countries.[5]

Among the factors associated with the likelihood of active TB risk, prior contact with an active TB patient was observed in 23 (3.0%), while fibrotic lesions compatible with LTBI were found in 84 (10.9%). In a study of 1097 kidney transplant patients, post-transplant TB incidence was reported as 2.1%, and previously healed TB on chest radiograph Relative rate 8.71, 95% CI 1.00-75.84, $P = .05$) was found as a significant pre-transplant risk factor for post-transplant TB on multivariate analysis.[15] Documentation of a detailed history including exposure to individuals with active TB in the household or workplace, prior TST results, and prior active TB is strongly recommended in the consensus reports.[13]

Post-transplant TB mostly develops from reactivation of latent TB infection, acquired primary infection has been reported in a small number of cases and donor-derived TB constitutes <5% of all TB cases.[6,13] Therefore, LTBI screening has critical importance and all transplant candidates including those with a history of vaccination with Bacillus Calmette–Guerin (BCG) should be screened. Tuberculin skin test and IGRAs have been used for this procedure; TST is the main diagnostic method recommended, however, IGRA tests may be the choice especially in countries endemic for TB and prior history of BCG vaccination as IGRA results are specific to M. tuberculosis antigens. Interferon-gamma releasing assay tests also have been shown to be more sensitive than end-stage renal disease or advanced liver disease, due to their high specificity.[16,17] Both tests may have false–negative or indeterminate results due to immunosuppressive drugs and some experts recommend using both TST and IGRA in high risk to maximize the sensitivity.[18,19] False negative results for TST are partly due to anergy related to end-stage organ disease and only 20% to 50% of active TB disease have been reported to have a positive TST before transplantation.[15,20] False–positive TST is mostly associated with prior vaccination with BCG or infection with other non-tuberculous mycobacteria.[21] In our study, the LTBI screening rate was in a wide range, however, it was relatively low overall (33.8%). Tuberculin skin test was the most frequently applied method due to cost and feasibility issues. The patients who developed posttransplant TB had not been given LTBI treatment despite two of them being positive.

Lung transplantation candidates were the ones with the lowest LTBI laboratory test positivity rates (31.1%) to whom 57.1% were offered LTBI treatment, while heart transplantation recipients were the most (83.3%), although none were offered treatment. Lung transplant recipients have been reported to have a greater risk of active TB, compared to other SOT recipients,[5,22] therefore LTBI treatment should be strictly administered in lung transplantation. More than half of the liver transplant candidates also had positive test results, however only one-third were offered LTBI treatment. Overall, LTBI screening test positivity was relatively high (46.9%) due to the heterogeneity of donated organs and the multicenter design. In another single-center study conducted on liver transplant recipients in Türkiye, a lower rate of 25.9% was reported.[23]

A positive TST and/or IGRA test demonstrates the presence of LTBI; however, a negative test does not exclude LTBI. Therefore, guidelines recommend screening all transplant candidates for TB by careful epidemiologic history, physical exam, and chest X-ray or thorax computed tomography, as well as TST or IGRA testing. A positive TST or IGRA should be considered for LTBI treatment after excluding active TB. Transplant candidates who have had recent exposure to a case of active TB and/or radiographic evidence of untreated TB are also recommended to be considered for LTBI treatment even in the case of indeterminate or negative TST or IGRA tests. Since donor-derived TB cases have been reported, all living donors should be screened, and transplant recipients who have received an organ from a donor with a positive TST should be offered.[13]

Although some cohorts defined that TB could still develop after treatment[24,25] recent evidence supports that LTBI treatment significantly reduces the incidence of TB reactivation in transplant recipients.[26] Isoniazid is the first-choice drug used for LTBI treatment; however, isoniazid-related hepatotoxicity is the main factor restricting the widespread use of INH, and only a quarter of SOT recipients have been reported to undergo LTBI treatment. There are studies reporting the safety of LTBI treatment with INH in liver transplant recipients; however, hepatotoxicity, drug interactions, and relatively low compliance rates of liver transplant recipients restrict implementation.[27,28] Recent guidelines recommend starting LTBI treatment after transplantation in decompensated cirrhosis.[13] In our study, the overall LTBI treatment recommendation was 60.8%, with the least (30.0%) in liver transplant recipients. Considering the risks of LTBI treatment might outweigh the benefits may be the reason for the low LTBI treatment recommendation rates in our study. Compliance of the liver transplant recipients was the lowest (19.4%), compatible with previous studies, and was the best in lung transplant recipients (62.5%) in our study. The compliance in lung transplant recipients may be better due to strict pulmonary disease follow-ups. Overall, LTBI treatment was completed in less than half of the patients, with a low compliance rate compatible with previous studies from different countries.[22,29] The reasons for these low completion rates might be listed as lost to follow-up, LTBI treatment-related adverse events, not applying to the dispensaries, etc. Latent tuberculosis infection treatment notification rates to the national registry were also lower than expected.

A separate section has been prepared for SOT recipients in the national TB diagnosis and treatment guidelines recommending LTBI screening for SOT recipients and donors after this study was terminated.[30]

One of the limitations of the study was that IGRAs had been studied in different centers with different commercial tests, but all the commercial kits were approved by national authorities.

Another limitation is that TST was applied and evaluated by different practitioners in different centers. However, when we look at the results in the national data network, we think that both TST and IGRA applications comply with the standards. The lack of LTBI screening or registration for donors was also a limitation. Routine administration of the BCG vaccine may also have influenced some TST results.

CONCLUSION

We found that approximately one-third of SOT recipients have been screened for LTBI depending on the pretransplant procedures of the transplantation center and transplanted organs. Laboratory tests were positive in half of the patients; however, LTBI treatment rates were different according to the donated organ between 30.0%-79.5%, and half of them were not registered. LTBI treatment completion rates were also relatively low, which might also be related to untracked processes caused by unregistered applications. All these findings indicate that LTBI screening and treatment in SOT recipients are inadequate and should be re-evaluated considering national recommendations.

Ethics Committee Approval: This study was approved by the Non-Invasive Research Ethics Committee of Dokuz Eylül University (approval number: 2014/28-13; date: September 4, 2014).

Informed Consent: An informed consent form is not required due to the fact that it is a retrospective study.

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