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Bronchiectasis in Türkiye: Data from a Multicenter Registry (Turkish Adult Bronchiectasis Database)

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Background: Bronchiectasis is a chronic lung disease characterized by permanent bronchial wall dilatation. Although it has been known as an orphan disease, it has recently gained attention because of registry-based studies and drug research.

Aims: We aimed to use a multicenter database to analyze and compare data regarding the etiology, associated comorbidities, microbiological characteristics, and preventive strategies of bronchiectasis in Türkiye to those of other countries.

Study Design: A multicenter prospective cohort study.

Methods: The multicenter, prospective cohort study was conducted between March 2019 and January 2022 using the Turkish Adult Bronchiectasis Database, in which 25 centers in Türkiye participated. Patients aged > 18 years who presented with respiratory symptoms such as cough, sputum, and dyspnea and were diagnosed with non-cystic fibrosis bronchiectasis using computed tomography were included in the study. Demographic information, etiologies, comorbidities, pulmonary functions, and microbiological, radiological, and clinical data were collected from the patients.

Results: Of the 1,035 study participants, 518 (50%) were females. The mean age of the patients was 56.1 ± 16.1 years. The underlying etiology was detected in 565 (54.6%) patients. While postinfectious origin was the most common cause of bronchiectasis (39.5%), tuberculosis was identified in 11.3% of the patients. An additional comorbidity was detected in 688 (66.5%) patients. The most common comorbidity was cardiovascular disease, and chronic obstructive pulmonary disease (COPD) and bronchiectasis was identified in 19.5% of the patients. The most commonly detected microbiological agent was *Pseudomonas aeruginosa* (29.4%). Inhaled corticosteroids (ICS) were used in 70.1% of the patients, and the frequency of exacerbations in the last year was significantly higher in patients using ICS than in nonusers ($p < 0.0001$). Age [odds ratio (OR): 1.028; 95% confidence interval (CI): 1.005-1.051], cachexia (OR: 4.774; 95% CI: 2,054-11,097), high modified medical research

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council dyspnea scale score (OR: 1,952; 95% CI: 1,459-2,611), presence of chronic renal failure (OR: 4,172; 95% CI: 1,249-13,938) and use of inhaled steroids (OR: 2,587; 95% CI: 1,098-6,098) were significant risk factors for mortality. Mortality rates were higher in patients with COPD than in those with no COPD (21.7-9.1%, p = 0.016). Patients with bronchiectasis and COPD exhibited more frequent exacerbations, exacerbation-related hospitalizations, and hospitalization in the intensive care unit in the previous year than patients without COPD.

Conclusion: This is the first multicenter study of bronchiectasis in Türkiye. The study results will provide important data that can guide the development of health policies in Türkiye on issues such as infection control, vaccination, and the unnecessary use of antibiotics and steroids.

INTRODUCTION

Bronchiectasis is a disease that is clinically characterized by cough and sputum and progresses to persistent dilatation and thickening of the bronchial wall.[1] Bronchiectasis, formerly regarded as an orphan and rare disease, has gained recognition in recent years.[2] There are registry-based studies on bronchiectasis in several countries, particularly in Europe.[3,4] According to the results of these studies, there are significant regional disparities in bronchiectasis between European countries and India.[5,6]

Türkiye acts as a bridge between Europe and Asia in terms of geography and culture and is socially influenced by both Europe and Asia. Although there are numerous studies on both adults and children conducted in Türkiye,[7,8] a multicenter database is yet to be established. The main hypothesis of the study is that the sociodemographic and clinical characteristics of patients with bronchiectasis in our country differ from those of more developed and underdeveloped countries. In this study, we aimed to examine the overall etiology, associated comorbidities, microbiological characteristics, and preventive strategies of bronchiectasis in Türkiye using a multicenter database created with the support of the Turkish Thoracic Society and compare the data with that from other countries.

MATERIALS AND METHODS

This study conducted between March 2019 and January 2022 used the Turkish Adult Bronchiectasis Database (TEBVEB), which received data from 25 centers in Türkiye. The centers included in the study were selected to represent the population of Türkiye (Figure 1).

The study methodology was announced by the Turkish Thoracic Society via e-mail, and researchers who were members of the Society were invited to participate in the study. The data form and study design were shared by identifying researchers who wanted to participate in the study and their centers. The study was approved by the Trakya University Faculty of Medicine Scientific Research Ethics Committee (approval number: 03/28, date: 19.02.2018, protocol number: TUTF-BAEK-2018/77). Patient information obtained from the centers participating in the study was recorded by creating a patient number.

FIG. 1. Provinces where the study centers are located.

Patients over the age of 18 years with respiratory symptoms such as cough, sputum, and dyspnea who had computed tomographic evidence of non-cystic fibrosis bronchiectasis were included in the study. Patients with cystic fibrosis, pediatric patients aged < 18 years, and those who did not consent to participate in the study were excluded from the study.

Exacerbation of bronchiectasis was defined as four or more of the following findings: change in sputum production, increase in dyspnea, increase in cough, fever > 38 °C, increase in wheezing, decrease in exercise tolerance, weakness, tremors, restlessness, decrease in respiratory function, and change in chest sounds or radiographic signs. The bronchiectasis severity index (BSI) was used to determine bronchiectasis severity. Using a combination of clinical, radiological, and microbiological features, BSI evaluates nutritional status, exacerbations, dyspnea symptoms, and radiological extent and is a strong predictor of bronchiectasis-related morbidity and mortality.[9] TEBVEB is an internet-based database where the demographic data of patients, etiology of bronchiectasis, accompanying comorbidities, pulmonary function test results, microbiological and radiological data, and treatment are recorded. Pulmonary function tests were performed according to international guideline recommendations.[10] Radiological data included the lobes affected by bronchiectasis and whether the involvement was bilateral or multilobar. Bronchiectasis was classified as cylindrical, varicose, or cystic bronchiectasis.[11] Patients were considered to be cachexic if they had a body mass index (BMI) of < 20 in the presence of chronic inflammation.[12] During patient follow-up, the time of events occurring within the last year was defined as "in the last year." Patient information was entered into the database prospectively in the form of initial admission and control data. Informed consent was obtained from the patients to participate in the registry-based study.

Statistical analysis

The conformity of data to normal distribution was tested using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare the

non-normally distributed variables between two groups, and Cohen's d effect size values were calculated to demonstrate the effect size. Relationships between categorical variables were examined using chi-square and Bonferroni multiple comparison tests. Variables found to be significant in the univariate analyses were evaluated using a multivariate backward stepwise logistic regression analysis to determine factors affecting mortality. SPSS Statistics for Windows (version 24; IBM) was used to perform all analyses, and a p-value of < 0.05 was considered statistically significant.

RESULTS

The study included 1,035 patients from 25 hospitals. The mean age of the patients was 56.1 ± 16.1 years, and 518 (50%) of them were female. Of the included patients, 616 (60.8%) had never smoked and 141 (13.9%) were current smokers. The underlying cause of bronchiectasis could be identified in 565 (54.6%) patients. Infection was found to be the cause of bronchiectasis in 409 (39.5%) patients, and a history of tuberculosis was discovered in 117 (11.3%) patients (Table 1).

Other than bronchiectasis, comorbidities were present in 688 (66.5%) patients. While cardiovascular diseases were the most common comorbidity, 19.5% of the patients demonstrated coexistent chronic obstructive pulmonary disease (COPD) and bronchiectasis (Table 2).

The most common symptoms at presentation were productive cough (62.3%) and dyspnea (62.5%). Of the included patients, 72.6% were admitted to the outpatient clinic with respiratory symptoms, 41.9% visited the emergency department, and 33.6% had been hospitalized in the previous year. Among the 988 patients whose treatment information could be accessed, 730 (73.9%) had used antibiotics in the previous year. The left lower lobe had the highest prevalence of bronchiectasis (n = 590, 57.1%). Cystic bronchiectasis was the most common type of bronchiectasis (n = 584, 56.4%). Samples were collected from 554 (58.1%) patients to isolate the microbiological agent. The causative agent was isolated in 246 (53.1%) of these samples. *Pseudomonas aeruginosa* was the most commonly detected microbiological agent in patients with bronchiectasis (n = 163, 29.4%). *Pseudomonas aeruginosa* was detected in 112 (20.2%) patients during the stable period. Examination for the presence of acid-resistant bacillus was performed on samples from 364 patients, and it was positive in six of them (1.6%). The culture report of these six patients revealed nontuberculous mycobacteria in three patients and *Mycobacterium tuberculosis* in three patients.

TABLE 1. Etiology of bronchiectasis.

Etiology	n	%
Known etiological factors	565	54.6
Postinfectious in origin	409	39.5
Tuberculosis history	117	11.3
Gastroesophageal reflux disease	99	9.6
Connective tissue disease	40	3.9
Inflammatory bowel disease	16	1.5
Primary ciliary dyskinesia	16	1.5
Immunodeficiency disease	13	1.3
Atypical mycobacterial disease history	2	0.2
HIV	2	0.2
Alpha-1 antitrypsin deficiency	2	0.2
ABPA	1	0.1

ABPA, allergic bronchopulmonary aspergillosis; HIV, human immunodeficiency virus.

Of the 844 patients whose treatment histories could be evaluated, 592 (70.1%) used inhaled corticosteroids (ICS) and 446 (52.9%) used mucolytics. As a clinical outcome parameter, exacerbation of bronchiectasis developed in 47.4% of the patients who had used ICS in the previous year and in 31.2% of the patients who did not use ICS ($p < 0.001$). Frequent exacerbations (> 2 per year) were more common in patients who used ICS than in patients who did not (41.9% vs. 30.8%). However, this difference was not statistically significant ($p = 0.076$). During the follow-up, the mortality rate was 14.8% among ICS and 4.2% among non-users. In addition to medical treatments, physiotherapy was administered to 173 (16.7%) patients, long-term oxygen therapy was administered to 140 (14.6%) patients, and surgical interventions were performed in 92 (9.6%) patients. The vaccination data of 840 patients was obtained. The influenza vaccine was administered to 343 (40.8%) patients, and the pneumococcal vaccine was administered to 402 (48%) patients.

The leukocyte count, neutrophil count, C-reactive protein level, and erythrocyte sedimentation rate were significantly higher, whereas the partial oxygen (PO_2), hemoglobin, and oxygen saturation levels were lower during the exacerbation periods than during the quiescent

TABLE 2. Comorbidities seen in patients with bronchiectasis.

Comorbidities	n	%
Presence of a comorbidity	688	66.5
Cardiovascular disease	250	24.2
Asthma	214	20.7
COPD	202	19.5
Diabetes mellitus	101	9.8
Malignancy	54	5.2
Anxiety	44	4.3
Depression	37	3.6
Thyroid disorders	30	2.9
Chronic renal failure	29	2.8
Neurological diseases	24	2.3
Osteoporosis	23	2.2
OSA	15	1.4
Cirrhosis	15	1.4
Nasal polyp	12	1.2
Rhinitis	11	1.1
Other comorbidities	217	21

COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

phase. Although the BSI high during the exacerbation periods, it was low in stable patients (Table 3). Patients with high modified medical research council (mMRC) dyspnea scale and BSI scores, patients with COPD, and patients with more frequent symptoms had a higher risk of exacerbation in the previous year (Table 4).

The rate of frequent exacerbations was significantly higher in patients with COPD than in patients without COPD (p = 0.036). Patients with bronchiectasis caused by childhood infections had a high exacerbation rate (p = 0.022).

Seventy-six (11.9%) of 638 patients with available mortality data died during the follow-up period. Variables with significant differences in the univariate analysis were age, presence of dyspnea and sputum in active complaints, cachexia, high mMRC level, high BSI score, presence of comorbidity, cardiovascular disease, COPD, and chronic renal failure, and malignancy history. These variables were included in the multivariate backward stepwise logistic regression analysis. Variables related to drug use were excluded from the regression analysis. Variables that were not significant for the model were

TABLE 3. Laboratory parameter results of patients during the stable and exacerbation periods.

Parameters	Exacerbation period (n = 379) Median (25%-75%)	Stable period (n = 628) Median (25%-75%)	Cohen's d	p
Leukocyte count (/µl, n = 928)	9360 (7250-11740)	8000 (6500-9815)	0.45	< 0.001*
Neutrophil count (/µl, n = 923)	6190 (4400-8800)	4660 (3510-6440)	0.58	< 0.001*
Hb (g/dl, n = 919)	12.8 (11.61-14.3)	13.2 (12-14.5)	0.24	0.002*
Urea (µmol/l, n = 716)	21 (13.5-34)	21 (14-30)	0.16	0.260
Creatinine (mg/dl, n = 778)	0.72 (0.59-0.87)	0.74 (0.61-0.89)	0.13	0.041*
GFR (ml/min, n = 638)	98 (84-116.48)	96 (83.7-113)	0.01	0.662
CRP (mg/l, n = 846)	11.8 (3.5-23.1)	3.8 (1-10)	0.67	< 0.001*
ESR (mm/hr, n = 428)	28.5 (13.5-50)	17 (7-33)	0.50	< 0.001*
IgE (IU/ml, n = 295)	48.2 (18.9-198)	41.2 (17-117)	0.15	0.226
PO_2 (mmHg, n = 304)	61.2 (53.1-77.6)	74.3 (62.4-89)	0.31	< 0.001*
SO_2 (%, n = 394)	93 (87-96)	96 (93.5-98)	0.58	< 0.001*
BSI (n = 779)	8 (4-11)	4 (2-7)	0.69	< 0.001*

BSI, bronchiectasis severity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; Hb, hemoglobin; IgE, immunoglobulin E; PO_2; partial oxygen pressure (arterial blood gas analysis); SO_2, oxygen saturation.

TABLE 4. Factors influencing exacerbations in the last year.

Factors		Group with exacerbation in the last year (n = 422) Median (25%-75%)	Group without exacerbations (n = 584) Median (25%-75%)	OR (95% CI)	p
Age		57.9 (44.5-68.5)	57.4 (43.7-68.4)	1 (0.99-1.01)	0.675
BMI		24.9 (21.5-29.3)	25.2 (22.3-29.3)	0.99 (0.96-1.01)	0.342
mMRC score		2 (1-3)	1 (0-2)	2.16 (1.87-2.48)	< 0.001*
Gender, n (%)	Male	211 (50)	289 (49.5)	1.02 (0.79-1.31)	0.872
	Female	211 (50)	295 (50.5)	1 (reference)	
Sputum, n (%)	Present	301 (72)	338 (59)	1.79 (1.36-2.34)	< 0.001*
	Absent	117 (28)	235 (41)	1 (reference)	
Dyspnea, n (%)	Present	335 (80.7)	305 (53.6)	3.62 (2.7-4.87)	< 0.001*
	Absent	80 (19.3)	264 (46.4)		
COPD, n (%)	Present	122 (28.9)	77 (13.2)	2.68 (1.95-3.68)	< 0.001*
	Absent	300 (71.1)	507 (86.8)	1 (reference)	
BSI group, n (%)	0-4	95 (27.9)	264 (61.5)	1 (reference)	
	5-8	85 (24.9)	106 (24.7)	2.23 (1.54-3.22)	< 0.001*
	≥ 9	161 (47.2)	59 (13.8)	7.58 (5.19-11.08)	< 0.001*

*p < 0.05 was considered significant in the univariate binary logistic regression analysis. BMI, body mass index; BSI, bronchiectasis severity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; mMRC, modified medical research council dyspnea scale; OR, odds ratio.

excluded and are not shown in the table. According to multivariate regression analysis, age, presence of cachexia (BMI < 20), high mMRC score, and presence of chronic renal failure were found to be significant risk factors of bronchiectasis-related mortality (Table 5).

Use of antibiotics in the previous year, mucolytics, intravenous steroids, ICSs, ipratropium, tiotropium, theophylline, and noninvasive mechanic ventilation were found to be significantly associated with mortality in the univariate analysis. These variable were included in the multivariate regression analysis, which revealed that ICS use (p = 0.030; OR: 2,587; 95% confidence interval: 1.098-6.098) was a significant risk factor for mortality.

Patients with COPD and bronchiectasis exhibited more exacerbations in the previous year, frequent exacerbations, exacerbation-related hospitalizations, and hospitalizations in the intensive care unit than patients with bronchiectasis without COPD. The etiology of bronchiectasis in patients with COPD, was most frequently an infection. Additionally, ICS use and antibiotic use in the previous year were more commonly found in patients with bronchiectasis and COPD than in patients without COPD. In terms of vaccination rates, Patients with COPD and bronchiectasis had a higher influenza vaccination rate, but no significant difference in pneumococcal vaccination rate than patients without COPD. The mortality rate was higher in patients with coexistent COPD and bronchiectasis than in patients with bronchiectasis but without COPD (Table 6).

DISCUSSION

This study is an important and pioneer study in terms of general clinical data of bronchiectasis in Türkiye and the reasons affecting mortality in this patient group. Bronchiectasis is a serious lung health issue, and this is the first national multicenter study conducted in Türkiye. In this study, the ratio of male to female was equal, and the average age of the study patients was 56 years. In a study conducted in Spain, bronchiectasis was detected in 54.9% of female patients, and the average age of the study participants was 64.9 years.[6] However, the average age of patients with bronchiectasis in India is reportedly 56 years, which is the same as that in our study, and 56.9% of the patients are males.[5] Infections, especially childhood infections, are considered a prominent cause of bronchiectasis in

TABLE 5. Non-treatment factors affecting mortality.

Variables		OR	95% CI	p
Age (years)		1.028	1.005-1.051	0.018*
Cachexia status	None (reference)			
	Present	4.774	2.054-11.097	0.001*
mMRC score		1.952	1.459-2.611	0.001*
Presence of CRF	None (reference)			
	Present	4.172	1.249-13.938	0.020*

*Multivariate backward stepwise logistic regression analysis. CI, confidence interval; CRF, chronic renal failure; mMRC, modified medical research council dyspnea scale; OR, odds ratio.

TABLE 6. Characteristics of patients with bronchiectasis with and without COPD.

	COPD and bronchiectasis (%)	Non-COPD bronchiectasis (%)	p
Male sex	69.3	45.3	< 0.001*
Age (years)	65.8 ± 11.3	53.7 ± 16.2	< 0.001*
Exacerbation in the last year	61.3	37.2	< 0.001*
Frequent exacerbations (> 2/year)	45.9	34.7	0.036*
Exacerbation-related hospitalization in the last year	51.8	29.2	< 0.001*
Hospitalization in the ICU due to exacerbation in the last year	17.2	3.9	< 0.001*
Infection as the etiology	50	37	< 0.001*
ICS use	44.2	22.7	< 0.001*
Oral steroid use	14.6	6.9	0.006*
IV steroid use	21.4	10.3	< 0.001*
Antibiotic use in the last year	83.6	71.5	< 0.001*
Influenza vaccination status	48.9	38.6	0.016*
Pneumococcal vaccination status	51.7	47.1	0.31
Mortality	21.7	9.1	0.016*

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ICS, inhaled corticosteroids; IV, intravenous.

Türkiye because the average age of the patients with bronchiectasis in Türkiye is relatively lower than that of patients in developed countries.

Although cystic fibrosis and HIV are the most common causes of bronchiectasis in developed countries, tuberculosis and other infections are the most common causes in underdeveloped or developing countries. In a study conducted in Spain evaluating patients with bronchiectasis but without cystic fibrosis, the etiology was identified in 75.8% of the patients, and infections were found to be the cause of bronchiectasis in 30% of the patients, which is similar to the findings in our study.[6] In another study, the etiology of bronchiectasis was determined in 60% of the 1258 included patients. Of the 1,258 patients, bronchiectasis was postinfectious in origin in 20% of the patients, 15% had coexistent COPD, and 10% had connective tissue diseases.[13] In an Indian study, the most common etiology of bronchiectasis was tuberculosis.[5] Etiological factors of bronchiectasis have been identified in approximately half of the studies conducted in Türkiye.[14] Among the detectable factors, the most common cause was found to be infections (15-69.7%), and tuberculosis has been detected at the rate of 12-25.3%.[15-18] In our study, infection was the cause in 39.5% of the patients, and the frequency of TB was 11.3%. Before the study was conducted we hypothesized that tuberculosis and infections as the etiology of bronchiectasis would be higher in Türkiye than in Europe. Infections was found to be the most frequent cause of bronchiectasis in our study; however, tuberculosis was detected at a rate of 11%. These rates indicate that we may have made progress in tuberculosis diagnosis and treatment. However, we believe that more effective policies should be followed, especially for childhood infections.

Comorbidities associated with bronchiectasis have a significant impact on mortality.[19] Recently, it has been suggested that the association between bronchiectasis and COPD should be evaluated as a separate entity and that bronchiectasis should be defined as COPD overlap syndrome.[20] Some studies have even emphasized that it may be a separate endotype.[21] COPD is the most common comorbidity identified in patients with bronchiectasis in studies conducted in Türkiye.[16,22] In our study, the most common comorbidity was cardiovascular diseases, and obstructive pulmonary diseases such as asthma and COPD ranked second. Because of the risk of more frequent exacerbations, hospitalizations, and mortality in patients with COPD than in patients without COPD, patients with COPD should be considered as a separate endotype in bronchiectasis.

Bronchiectasis is most commonly observed in the lower lobes, especially in the left lower lobe.[5,17] In our study, bronchiectasis was found most frequently in the left lower lobe. Chronic infections and colonization are common in bronchiectasis. *Pseudomonas aeruginosa* and *Haemophilus influenzae* are the most common agents associated with bronchiectasis.[23] *Pseudomonas* infections in bronchiectasis increase the mortality rate by three times and hospital admission rates by seven times.[24] The agent detection rate of bronchiectasis in Türkiye is between 40% and 60%, and the most commonly detected agents are *Pseudomonas aeruginosa* (25-30%) and *Streptococcus pneumoniae*.[8,25] It is recommended that all patients with bronchiectasis undergo a microbiological assessment to identify the causative agent.[26] The COVID pandemic emerged during this study, and the effort to detect microbiological agents shifted to COVID detection. Therefore, samples of only half of the patients were sent for microbiological examination, and the agent was isolated in only half of them. Among the isolated agents, *Pseudomonas aeruginosa* was most frequently detected.

In this study, the influenza and pneumococcal vaccination rates were 40%. In a study in Spain, the influenza vaccination rates was 30%, and pneumococcal vaccination rates were 16%.[27] The higher pneumococcal vaccination rates in our study may be because our study period coincided with the pandemic period. Although the vaccination rates in our study were higher than those of other studies and the general population in Türkiye, we think that these rates should be increased further with patient-physician cooperation. The BSI score is associated with mortality.[28] In our study, the BSI was found to affect both mortality and emergency department admissions.

In our study, the mortality rate was 11.9% among patients whose data could be accessed. In another study conducted in Türkiye, the mortality was 16.3%.[29] In our study, age, cachexia, a high mMRC score, and the presence of comorbidities were found to be significant factors affecting mortality. In another study conducted in Türkiye, a high mMRC score was found to be an independent factor affecting mortality.[30] In another study, the presence of comorbidities and *Pseudomonas aeruginosa* colonization were identified as factors affecting mortality[31] We hope that consumption of protein-rich meals and the early and effective treatment of comorbidities and infections can reduce mortality in patients with bronchiectasis.

The main limitation of our study is that although it was a prospective study, the emergence of the COVID-19 pandemic during the study period disrupted the follow-up of some patients. Some study participants, who initially agreed to participate in the study and represented all regions of Türkiye, could not participate due to the pandemic. Furthermore, during patient follow-up, risky procedures in terms of contamination, such as respiratory function tests, could not be performed.

In this study, we determined that our patients with bronchiectasis were younger than those in Europe and were in the same age range as those in India. In addition, there was no difference between males and females. It was observed that the etiology of bronchiectasis of majority of our patients was infections. Although the comorbidities such as COPD and asthma were diagnosed in 20% of the patients, the use of ICS was found to be very high, indicating that some of the patients may have been unnecessarily administered steroids. Compared with more developed countries, infectious causes of bronchiectasis played an important role in both the development of bronchiectasis and the associated complications in Türkiye. However, this can be prevented with socioeconomic development throughout society. The rate of tuberculosis as the etiology of bronchiectasis in Türkiye was lower than expected. Excessive medication use in patients constitutes another public health problem and an economic burden on the health system, and precautions should be taken to avoid this. Multicenter studies such as ours, which can

guide the development of health policies in Türkiye, could provide important data on issues such as infection control, vaccination, and unnecessary use of antibiotics and inhaled or systemic steroids.

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