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Original Article

Current Status of Cystic Fibrosis in Türkiye: Data from the National Registry

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Abstract

OBJECTIVE: The Cystic Fibrosis Registry of Türkiye (CFRT) was established by the Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society and has provided detailed information on demographic, clinical, genetic, and treatment-related aspects of cystic fibrosis (CF) patients since 2017. We aimed to describe the current status of CF in Türkiye using CFRT's 2023 annual data.

MATERIAL AND METHODS: Demographic, clinical, and treatment data were taken from CFRT's 2023 record.

RESULTS: In 2023, 2,258 patients from 34 centers were recorded. The median age of patients was 9.1 years, and 46.9% were female, with a median age at diagnosis of 0.3 years. Only 14.9% of the patients were older than 18 years. Genetic analyses were completed in 97.3% of patients. The most common variant, F508del, had a total variant frequency of 22.1%. The median percent predicted FEV1 and FVC were 88.0 and 94.0 in those aged 6-17 years 71.0 and 84.0 in those aged ≥18 years, respectively. The median values of body mass index z-scores were -0.5, and -0.5 for patients 2-18 and older than 18 years, respectively. Chronic colonization with *Pseudomonas aeruginosa* was present in 17.2% of the patients. Most patients used inhaled recombinant human DNase (87.1%) and oral pancreatic enzyme replacement treatment (83.0%). CF transmembrane conductance regulator (CFTR) modulators were used by 15.9% of patients. Over the year, 24 patients died, with a median age at death of 13.3 years.

CONCLUSION: The CFRT report provides a valuable resource showing the clinical and laboratory data of patients with CF in the country.

KEYWORDS: Cystic fibrosis, Cystic Fibrosis Registry of Türkiye, annual data

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INTRODUCTION

Cystic fibrosis (CF) is caused by autosomal recessive mutations in the gene that codes for the CF transmembrane conductance regulator (CFTR) protein.[1] CFTR dysfunction causes multi-organ disorders, including chronic sino-pulmonary infections with bronchiectasis, exocrine pancreatic insufficiency, malabsorption, growth failure, distal intestinal obstruction syndrome, and infertility, all of which vary in prevalence.[1,2]

Patient registries are structured systems for gathering comprehensive data, including sociodemographic, clinical, and other important information from various healthcare sources.[3] Registry data fosters partnerships between patients, families, and healthcare providers. They are vital for rare diseases like CF as they unify standardized individual data from various clinics and countries, enabling more robust statistical analyses and optimizing resource use.[4] The first CF registry was launched in the United States of America (USA) in 1966.[5] While many countries established national CF registries,[6-9] international CF patient registry systems were established.[10] Cystic Fibrosis Registry of Türkiye (CFRT) was established by the Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society in 2007.[11] In CFRT, after obtaining written informed consent from parents and patients, each center records patients' demographic and annual data in a software program specifically developed for the CFRT. The first comprehensive results of this national registry were published, with the demographic and laboratory data collected from 1,170 registered patients from 23 centres in 2017.[11,12] The CFRT has been contributing to the European Cystic Fibrosis Society's Patient Registry (ECFSPR) since 2016.[13] Many studies were conducted using CFRT data to evaluate the relationship between follow-up, clinical features, growth, treatment, and complications of patients.[14-21]

This review aims to describe the current status of CF in Türkiye by using the 2023 annual data of CFRT.[22]

MATERIAL AND METHODS

This retrospective study included individuals with CF represented in the 2023 CFRT data. The diagnosis of CF was established based on typical clinical findings, with at least two positive sweat chloride tests and/or two CF-causing CFTR mutations.[23]

Demographic and annual data, including sex, age at diagnosis, current age, z-scores of weight, height, and body mass index (BMI), results of neonatal CF screening, pulmonary function tests, history of meconium ileus, medications, presence of microorganisms, complications, and transplantations, were recorded.

The z-scores of all individuals for weight and height were recorded, while BMI and BMI z-scores were noted for those over the age of 2. The bacterial colonization status is considered chronic if more than 50% of respiratory samples test positive over a 12-month period.[24]

Each center records patient data annually in a specially developed software program for the CFRT. At the end of each year, the CFRT board members review and clean the registry data. After correcting and excluding missing data, CFRT analysts performed a descriptive analysis and provided the variable changes by year. We obtained the descriptive annual data for 2023 from the CFRT database.

The study was conducted after approval from the Hacettepe University Faculty of Medicine Institutional Research and Ethical Committee (reference numbers: GO 23/469, date: 06.06.2023) and according to the Declaration of Helsinki guidelines. Written informed consent from participants' parents and age-appropriate assent from all participants were obtained annually before participants were included in the registration system.

Statistical Analysis

Statistical analysis was performed by the Pleksus company (Türkiye). Missing data were excluded from the analysis. Findings from descriptive analyses were reported as relative and absolute frequencies for categorical variables, and as median and quartile values for quantitative variables.

RESULTS

Demographics

In 2023, 2,258 individuals with CF were registered at 34 centers in Türkiye, which we estimate cover over 70% of CF patients in our country. The number of registered individuals with CF in 2022 was 2,088. One thousand fifty-eight individuals (46.9%) were females, and the patients' median current age was 9.1 years (with a range of 3 months to 48.8 years). Table 1 gives the demographic characteristics of patients. Adults accounted for 14.9% (n = 336) of the CF population.

The number of CF centers contributing to the registry system has increased from 20 to 34 (Figure 1a). The number of patients in the system has gradually increased (Figure 1b), and the number of adult patients reporting has risen from 9 to 336 from 2016 to 2023. Pediatricians still follow most patients with CF in most centers (18/34) in Türkiye, and the transition to adult clinics has just been implemented in many other centers. However, only three adult CF centers (8.8%) contributed data to CFRT. Figure 2 shows a map of cities that contributed data in 2023.

Diagnosis

The median age of our patients at diagnosis was 0.3 years; the oldest was 41 years (Table 1). Seventy-eight percent of patients ≤7 years of age in 2023 were diagnosed through NBS. 4.7% of our patients, currently aged ≤10 years, were diagnosed with meconium ileus.

Genetics

In 2023, genetic analyses of our registered patients were completed in 2196 (97.3%) individuals with CF. Among genotyped patients, two variants were identified in 1916 patients (84.9%), one variant was identified in 155 patients (6.9%), and no variants were found in 125 patients (5.5%). The most common variant was F508del, which had a total allele frequency of 22.1%. The prevalence of the F508del mutation in homozygous form was 12.1% (266 individuals), and in F508del heterozygous form was 15.9% (349 individuals) among individuals whose genetic analyses were completed. The distribution of the 15 most common variants in genotyping is given in Figure 3.

Lung Function

In 2023, the lung function of 1,020 patients (45.2%) was recorded, 755 of whom were between 6 and 17 years old, and 265 were 18 and older. The median percent predicted (pp) FEV1 and FVC were 88.0% and 94.0% in individuals with CF aged between 6 to 17 years and 71.0% and 84.0% in those aged ≥18 years, respectively. Table 2 shows the distribution of categorical pp FEV1 values. The distribution of the median pp FEV1 by age group is given in Figure 4.

Microbiology

Among all patients, 17.2% had chronic infection with *Pseudomonas aeruginosa*, 14.8% with methicillin-sensitive *Staphylococcus aureus*, 10.3% with methicillin-resistant *Staphylococcus aureus*, and 1.3% with *Haemophilus influenzae*. Figure 5 shows the prevalence of chronic and intermittent *Pseudomonas aeruginosa* by year.

The prevalence of *Burkholderia cepacia* complex chronic infection was 0.4%, and intermittent infection was 0.1%. Non-tuberculous mycobacterial infection was seen in 17 (0.8%) patients. The prevalence of patients with chronic infection with *Stenotrophomonas maltophilia* was 0.1%, while intermittent infection was 0.8%. Chronic infection with *Achromobacter* species was reported in 8 (0.4%) patients, and intermittent infection was reported in 13 (0.6%) patients.

Main Points

- Patient registry data fosters partnerships between patients, families, and healthcare providers.
- By 2023, 2,258 registered cases from 34 centers, which we estimate cover over 70% of cystic fibrosis (CF) patients in our country.
- Adults accounted for 14.9% of the CF population. Pediatricians still follow most patients with CF in most centers (18/34), in Türkiye.
- Educating clinicians, patients, and families about the registry's importance in improving CF care and increasing the number of adult CF centers would facilitate greater compliance with the Cystic Fibrosis Registry of Türkiye (CFRT).
- The CFRT report provides a valuable resource showing the clinical and laboratory data of patients with CF in the country.

Table 1. Demographic characteristics of registered patients in 2023

	Female	Male	Total
Total registered patients n (%)	1,058 (46.9)	1,200 (53.1)	2,258 (100.0)
Current age, median (Q1-Q3), years	8.5 (4.6-14.3)	9.7 (5.4-15.4)	9.1 (5.1-14.9)
Age at diagnosis, median (Q1-Q3), years	0.3 (0.2-0.9)	0.3 (0.2-1.0)	0.3 (0.2-1.0)
Number of patients aged ≥18, n (%)	143 (13.5)	193 (16.1)	336 (14.9)
Number of patients who died in 2023, n (%)	17 (1.6)	7 (0.6)	24 (1.1)
Ages at death, median (Q1-Q3), years	14.2 (5.2-19.2)	12.3 (7.6-15.8)	13.3 (5.8-18.8)

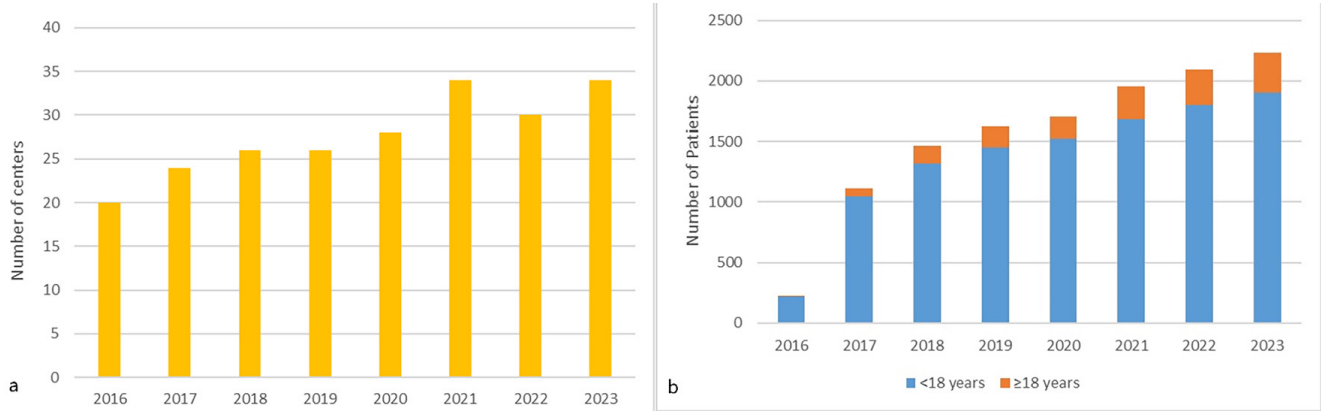

Figure 1. (a, b) Number of CF centers contributing to the registry by year, and number of patients under and over the age of 18 by year

CF: cystic fibrosis

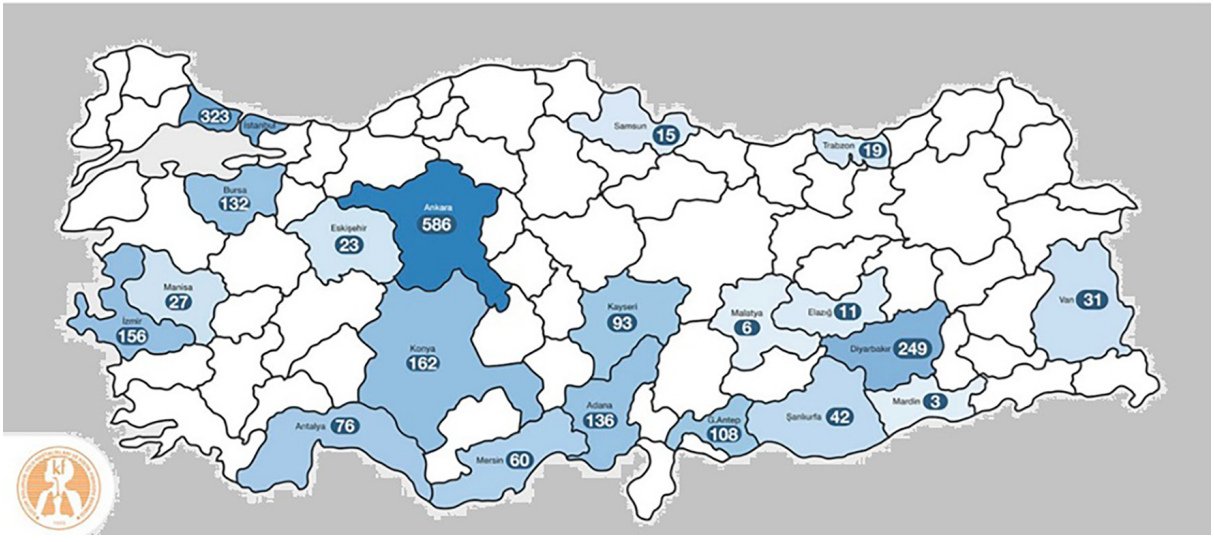

Figure 2. Map of cities that contributed data in 2023

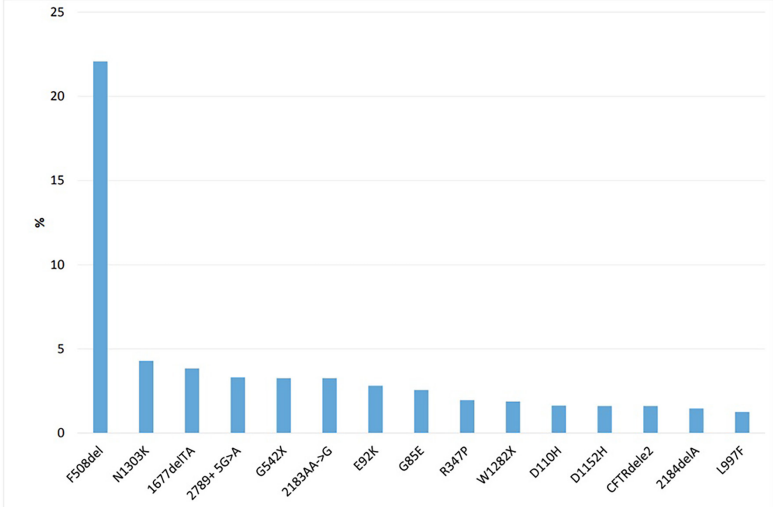

Figure 3. Distribution of the 15 most common variants

Table 2. Distribution of categorical pp FEV1

Age	pp FEV1			
	≤40%	41-59%	60-79%	≥80%
6-17 years n (%)	29 (3.8)	61 (8.1)	162 (21.5)	503 (66.6)
≥18 years n (%)	50 (18.9)	47 (17.7)	63 (23.8)	105 (39.6)

pp: percent predicted

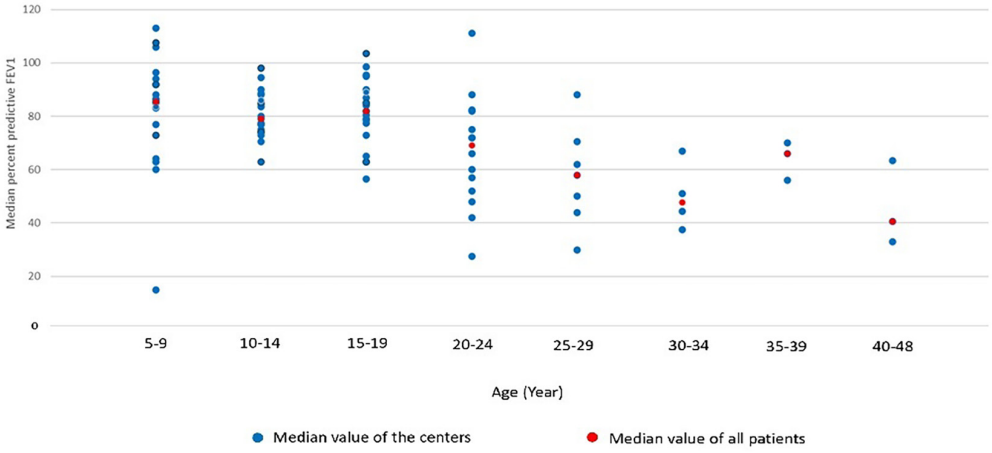

Figure 4. Distribution of the median FEV1 percentage by age group

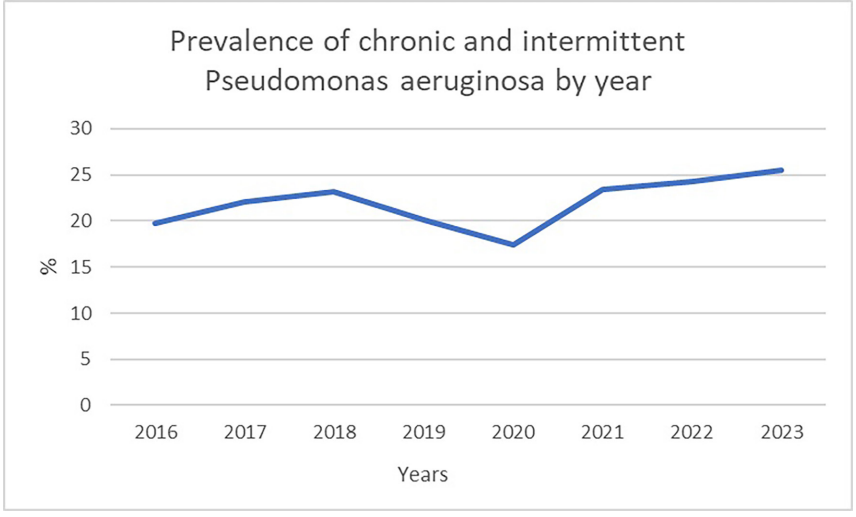

Figure 5. Prevalence of chronic and intermittent *Pseudomonas aeruginosa* by year

Nutrition

In 2023, 83.0% of our registered patients with CF were pancreatically insufficient. The median body weight, height, and BMI z-scores were -0.7 (Q1: -1.3- Q3: 0.0), -0.6 (Q1: -1.6- Q3: 0.3), and -0.5 (Q1: -1.1- Q3: 0.2) in patients under 18 years and -0.7 (Q1: -1.4- Q3: -0.6), -0.6 (Q1: -1.2- Q3: 0.1) and -0.5 (Q1: -1.1- Q3: 0.2) in patients 18 and older, respectively. Figure 6 shows the distribution of median body weight and height z-scores according to age groups and centers. Percutaneous endoscopic gastrostomy was preferred in 12 patients (0.5%) as a feeding and nutritional support route.

Complications and Hospitalizations

Four hundred fifteen patients (18.4%) received intravenous antibiotics for acute pulmonary exacerbations in the hospital for at least one day. Except for routine check-ups, 612 patients (27.1%) spent at least one day in the hospital.

Table 3 summarizes all complications related to CF. The most common complication was liver disease, followed by gastroesophageal reflux.

Treatments

Table 4 summarizes all treatments given to our patients. Most of the patients used recombinant human DNase (87.1%), pancreatic enzyme replacement (83.0%), and multivitamins (71.5%). More than half (58.2%) of the patients received oral nutritional supplements. The prevalence of azithromycin use as a prophylactic antibiotic, and anti-inflammatory treatment was 10.3%. Thirty patients (1.3%) used oral steroids.

CFTR modulators have been used in our country since 2021. Among the patients eligible for modulatory treatment, 358 (15.9%) used CFTR modulators, with elexacaftor/tezacaftor/ivacaftor being the most preferred. The number of patients using CFRT modulator therapy was 35 in 2021 and 358 in 2023. Table 5 shows the number of patients using modulators yearly in all centers. Due to our country's high diversity of mutations and the lack of drug reimbursement, a limited number of patients are eligible for modulator treatments, resulting in a frequency of 15.9% for modulator use.

Transplantation and Mortality

Six CF patients were living in 2023 with transplanted lungs, two with transplanted livers, and one with transplanted kidneys.

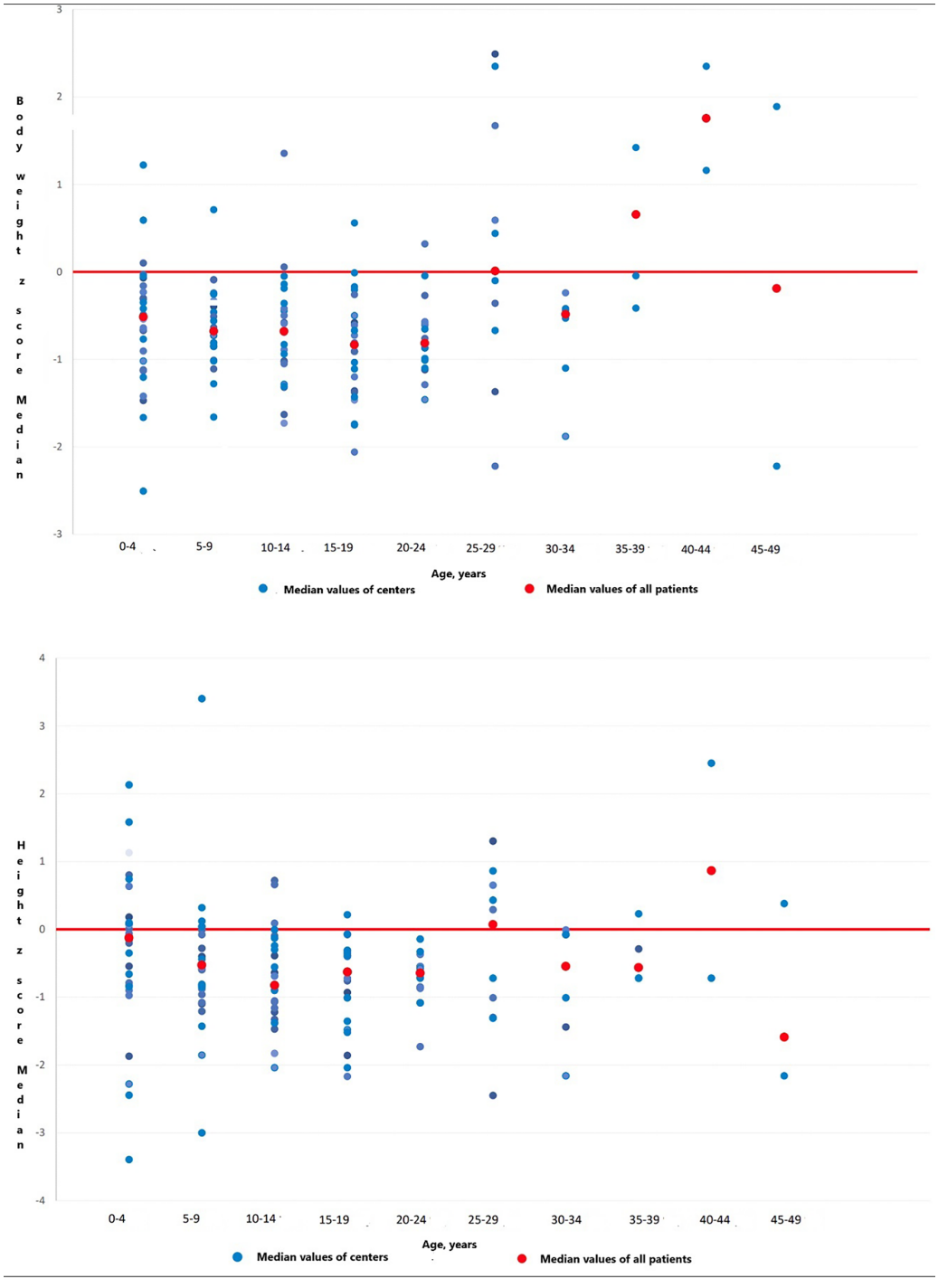

Figure 6. Distribution of median body weight and height z-scores: according to age groups and centers

The deaths of 24 of our patients were documented over the year, all but one of whom died from respiratory problems. Our patients' median age at death was 13.3 years (ranging from 1 to 17 years), and 17 were female.

Table 3. Complications

Complication	n (%)
Pulmonary	
Allergic bronchopulmonary aspergillosis	42 (1.9)
Massive hemoptysis (≥250 mL over the course of a day)	16 (0.7)
Pneumothorax	10 (0.4)
CF-related diabetes	
Using Insulin	96 (4.3)
Only on diet	31 (1.4)
Therapy unknown	4 (0.2)
Liver diseases	
Liver disease without cirrhosis	394 (17.5)
Cirrhosis with portal hypertension/hypersplenism	21 (0.9)
Cirrhosis without portal hypertension/hypersplenism	6 (0.3)
Other complications	
Sinusitis	197 (8.7)
Gastroesophageal reflux	125 (5.5)
Pseudo-Bartter's syndrome	90 (4.0)
Osteoporosis	66 (2.9)
Distal intestinal obstruction syndrome	29 (1.3)
Malignancy	4 (0.2)

CF: cystic fibrosis

Table 4. Treatments for ≥3 consecutive months

Pulmonary treatments	n (%)
rhDNase	1966 (87.1)
Inhaled bronchodilator	700 (31.0)
Hypertonic saline	545 (24.1)
Inhaled antibiotics	455 (20.2)
Inhaled steroids	318 (14.1)
Oxygen support	67 (3.0)
Mannitol	63 (2.8)
Non-invasive mechanical ventilation	56 (2.5)
Gastrointestinal system treatments	
Pancreatic enzyme replacement	1875 (83.0)
Multivitamins	1615 (71.5)
Oral nutritional supplements	1315 (58.2)
Proton pump inhibitors	357 (15.8)
Ursodeoxycholic acid	346 (15.3)
CFTR modulator therapies	
Elexacaftor/tezacaftor/ivacaftor	279 (12.4)
Ivacaftor	55 (2.4)
Lumacaftor/ivacaftor	17 (0.8)
Tezacaftor/ivacaftor	7 (0.3)

CFTR: cystic fibrosis transmembrane conductance regulator, rh: recombinant human

DISCUSSION

This review aims to summarize CFRT 2023's annual data, as it contains the most comprehensive and detailed information about CF patients in our country.[22] The annual data report includes data from individuals diagnosed with CF who have consented to participate in the CFRT and were seen in a CF center during the 2023 calendar year. These data allow us to compare various clinical practices, understand differences, and optimize treatment between CF centers.

It is estimated that there are more than 180,000 people with CF worldwide. CF was initially considered a primary childhood disease. However, improvements in care have led to a substantial and growing adult population. The incidence of CF is the same in female and male individuals.[1-3]

In 2023, the median age of patients with CF in the USA was 22.5, and it was 9.1 in our country.[22,28] According to annual data for 2022-2023, more than half of the people with CF are over 18 years old in the USA and Europe.[27,28] The number of registered patients with CF in the CFRT continues to increase, as does the number of registered adults; however, the proportion of adults is still less than 25%.[22] Only three adult centers (8.8%) care for adult CF patients, who contribute data to CFRT. Pediatricians still follow most patients with CF in most centers (18/34) in Türkiye, and the transition to adult clinics has just been implemented in many centers. The increasing contribution of adult CF care centers in the registry will accurately reflect the number of adult CF patients in the country. Our number of adult patients is low compared to Europe and the USA, and our adult CF centers are also limited. This may be due to insufficient knowledge among adult chest physicians about CF disease and the lack of structured transition programs to support the appropriate shift from pediatric to adult clinics. To address this issue, it is essential to provide training programs for both pediatric and adult chest physicians. Educating clinicians, patients, and families about the registry's importance in improving CF care and increasing adult CF centers would facilitate greater compliance with CFRT.

CFRT includes most CF centers nationwide, except for a few that provide their patients' information directly to the ECFSPR. In our national registry data published in 2020, there were only 1,170 registered patients, and we estimated the coverage rate to be 30% of the entire CF population in the country.[12] By 2023, we had 2,258 registered cases, which we estimate cover over 70% of CF patients in our country.[22]

The diagnosis of CF is based on typical features, a family history of CF, or a positive newborn screening (NBS) test associated with evidence of CFTR dysfunction.[1,2] The CF diagnostic criteria are two sweat tests greater than 60 mmol/L chloride and/or two

Table 5. Patients using modulators by year in all centers

Year	Ivacaftor, n	Lumacaftor-ivacaftor, n	Tezacaftor-ivacaftor, n	Elexacaftor-tezacaftor-ivacaftor, n
2021	3	2	6	24
2022	20	10	8	124
2023	55	17	7	279

identified disease-causing CF variants, one on each parental allele.[1]

The diagnosis of CF is established upon typical clinical findings, with two positive sweat chloride tests and/or two CF-causing CFTR variants.[1,2] The age of diagnosis in many countries has shifted to the first 3 months of life with the implementation of NBS.[22,27,28] NBS for CF has been implemented in our country since 2015, and two repeated immunoreactive trypsinogen (IRT/IRT) tests are used.[10] Meconium ileus at birth is not rare and may be the first symptom of CF detected in newborns.[1,2] Approximately 15% of infants with CF are born with meconium ileus.[2] In CFRT, the rate of meconium ileus in patients under 10 years old is almost 5%. The overall rate is likely higher when considering all patients. However, this difference may be due to limited awareness of CF in some healthcare centers, which can lead to underreporting, especially regarding early-onset manifestations that occur in the neonatal period (patients might die before diagnosis). These cases may not be systematically recorded or linked to later CF diagnoses. Additionally, patients may receive treatment at centers that do not contribute data to the CFRT. Furthermore, false-negative NBS results may frequently arise in patients with meconium ileus, potentially influencing the observed outcome rates.

The *CFTR* gene has been found to contain more than 2,000 variants, some with virtually no CFTR function and others associated with residual function.[26] The most common CFTR variant is F508del in Europe and the USA.[3]

Most individuals with CF have two identified CFTR variants, with the most common mutation being F508del in all registries.[22,27,28] The most common CFTR variant, F508del, is seen in more than 80% of the USA and Europe;[27,28] however, it remains 22% in our country.[22] These differences indicate that Turkish CF patients have a different mutation spectrum from others. Türkiye's high prevalence of consanguineous marriages and geographical location between Asia and Europe has the potential for immigration, and as a result, it contains racially and ethnically diverse populations, which may explain the difference.

Lung disease is the primary cause of morbidity and mortality in CF. The natural course of the disease suggests a 1-2% decline in pp FEV1 annually.[1-3] The median pp FEV1 value is higher in many European countries and the USA than in our country in all age groups.[22,27,28]

Host defense defects in inflammatory cells and impaired mucociliary clearance increase the risk of airway infections in people with CF.[2] The chronic nature of these infections worsens lung disease. One of the most frequent pathogens isolated in the CF airways is *Pseudomonas aeruginosa*, and its chronic colonization is associated with a worse prognosis.[1-3]

Pseudomonas aeruginosa and *Staphylococcus aureus* are still predominant respiratory pathogens in individuals with CF.[22,27,28] The prevalence of Pseudomonas aeruginosa infection has decreased in the CF population in Europe and the USA since the increased usage of CFTR modulators.[26,27] However, we did not detect a significant change in the prevalence of *Pseudomonas aeruginosa* infection.[22] The prevalence of intermittent and chronic *Pseudomonas aeruginosa* was lowest in 2020. The Coronavirus disease-2019 pandemic may have contributed to this, as patients did not visit the hospital to provide airway culture samples. The slight increase in the prevalence of intermittent and chronic *Pseudomonas aeruginosa* in recent years can be attributed to the development and maturation of CFRT, the sharing of registry data, heightened awareness among centers about these infections, and improved diagnostic capabilities in their laboratories.

Up to 90% of individuals with CF have exocrine pancreatic insufficiency,[1,2] as most of our patients are pancreatic insufficient.[22] Because of inadequate intake, increased energy expenditure, and malabsorption, patients with CF are at risk of malnutrition. The degree of underweight in CF patients negatively affects survival. Early assessment and management of nutritional status are vital to positively influence lung function in CF patients. Prevention of malnutrition should be a key focus in treating all CF patients.

Most patients with CF (85-90%) have exocrine pancreatic insufficiency. Exocrine pancreatic insufficiency is diagnosed by the presence of low fecal elastase levels, along with typical signs such as fatty stools, flatulence, and poor weight gain.[1,2] It results in maldigestion, malabsorption of nutrients, steatorrhea, fat-soluble vitamin deficiency, and malnutrition. Malnutrition was one of the most important causes of death before pancreatic replacement enzyme therapy.[1,2]

Our patients' height, weight, and BMI values are lower than in many European countries and the USA.[22,27,28] Increased early diagnosis of CF patients through NBS and increased usage of CFTR modulators may allow these patients in our country to have better nutritional metrics, similar to those in Europe and the USA.

Symptomatic treatment, prophylactic treatment, and response to acute events have been applied since the disease was described.[2] With a better understanding of CF, symptomatic treatments and new drugs have steadily been developed. Symptomatic CF treatments include maintaining good nutrition, pancreatic replacement therapy, regular chest physiotherapy, and the inhalation therapy of mucolytic agents to improve mucociliary clearance. They also include prophylactic and aggressive treatment of pulmonary infections with inhaled, oral, and intravenous antibiotics and early identification and treatment of complications.[1,2]

The new treatments that improve CFTR function are called CFTR modulators. CFTR modulators comprise two classes: potentiators and correctors. Ivacaftor was launched as a potentiator in 2012; combinations of potentiators and correctors have emerged, such as lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor. CFTR modulators are currently licensed and used in many countries.[1,2] Those are oral agents that bind to the CFTR protein.[1-3] CFTR modulators have been shown to improve BMI, reduce sweat chloride concentrations, increase predicted FEV1%, quality of life, and decrease pulmonary symptoms.[1,2] CFTR modulators are used in patients with eligible genetic variants and who meet age criteria. Approximately 90% of patients in the USA and 73% of patients in Europe are eligible for CFTR modulators;[27,28] however, less than 20% of our

patients can use CFTR modulators in our country due to the diversity of mutations, the limited number of patients eligible for modulator treatments and the lack of drug reimbursement limit our country's frequency of modulator use.[22]

The increased use of modulatory treatments, which have been shown to have many positive effects on the quality of life and life expectancy of CF patients, and the increase in the number of adult CF centers, will improve our patients' outcomes. However, due to our wide range of mutations, new treatment modalities are still needed for our patients, especially those not eligible for modulator treatments.

The incidence of CF is the same in females and males, but there is a survival difference. The lower survival of females with CF compared to males with CF contrasts with the longer survival of females than males in the general population.[2] Most deaths in people with CF occur between the third and fifth decades of life in Europe and the USA. Unfortunately, most deaths are still most common in the first decade in our country.[22,27,28] The limited opportunities for transplantation and limited use of CFTR modulators are among the reasons for earlier deaths in our country. As noted in the literature, the higher mortality rate was observed in females compared to males. This can be attributed to various factors, including physiological, biochemical, nutritional, and behavioral differences. Female lung anatomy may contribute to smaller lung volumes and less effective airway mucus clearance. Pulmonary exacerbations and mortality rates are comparable between boys and girls before puberty, suggesting that female hormones may influence airway pathophysiology. Nevertheless, female sex remains an independent risk factor for death.[29]

The report has several limitations. First, a few CF centers in Türkiye do not provide their data to CFTR. Thus, some CF patients remain unregistered. Second, analyzing registry-based data may not allow us to interpret causality. Additionally, there is no auditing for data accuracy and completeness. However, CFTR has initiated a new program to verify and validate data at its source in participating centers. This program aims to quantify data completeness, consistency, and accuracy. Despite these limitations, the report provides Türkiye's most comprehensive and detailed information on individuals with CF.

CONCLUSION

In conclusion, this study provides our country's most comprehensive and detailed information about individuals with CF. CFRT reports provide critical insights into CF management resources for improvement nationwide.

Ethics

Ethics Committee Approval: The study was conducted after approval from the Hacettepe University Faculty of Medicine Institutional Research and Ethical Committee (reference numbers: GO 23/469, date: 06.06.2023) and according to the Declaration of Helsinki guidelines.

Informed Consent: Written informed consent from participants' parents and age-appropriate assent from all participants were obtained annually before participants were included in the registration system.

Footnotes

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: All authors contributed equally to all contribution sections.

Conflict of Interest: No conflict of interest was declared by the authors.

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