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Cystic fibrosis in Turkey: First data from the national registry

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Abstract

Background: Cystic fibrosis (CF) care has been implemented in Turkey for a long time; however, there had been no patient registry. For this purpose, the Turkish National CF Registry was established. We present the first results of registry using data collected in 2017.

Methods: The data were collected using a data-entry software system, which was accessed from the internet. Demographic and annually recorded data consisted of 15 and 79 variables, respectively.

Results: There were 1170 patients registered from 23 centers; the estimated coverage rate was 30%. The median age at diagnosis was 1.7 years (median current age: 7.3 years); 51 (4.6%) patients were aged over 18 years. Among 293 patients who were under 3 years of age, 240 patients (81.9%) were diagnosed through newborn screening. Meconium ileus was detected in 65 (5.5%) patients. Genotyping was performed in 978 (87.4%) patients and 246 (25.2%) patients' mutations were unidentified. The most common mutation was deltaF508 with an allelic frequency of 28%, followed by N1303K (4.9%). The median FEV1% predicted was 86. Chronic colonization with *Pseudomonas aeruginosa* was seen in 245 patients. The most common complication was pseudo-Bartter syndrome in 120 patients. The median age of death was 13.5 years in a total of 15 patients.

Conclusions: Low coverage rate, lack of genotyping, unidentified mutations, and missing data of lung functions are some of our greatest challenges. Including data of all centers and reducing missing data will provide more accurate data and help to improve the CF care in Turkey in the future.

KEYWORDS
cystic fibrosis, national registry, patient registry

1 | INTRODUCTION

Patient registries allow physicians, researchers, and policymakers to examine data for trends and clinical outcomes among patients and to investigate the natural history of a disease for patients.[1] Cystic fibrosis (CF) national registries have been developed in many countries by bringing patient data together from specialist CF centers.[2] CF care has long since been implemented in Turkey in many clinics. The first report on CF in Turkey was published in 1973, in which the first prevalence of CF was determined as 1/3000 using sweat chloride tests.[3] In a recent report, the incidence of CF was found as 2.9 per 10 000 live births in Central Anatolia.[4] However, there had been no CF patient registry in the country. To better understand the demographics of CF in Turkey, the CF Registry of Turkey (CFRT) was established by the "Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society." In this report, we aim to describe the establishment of the CFRT and demonstrate the first comprehensive analysis of Turkish patients with CF registered in 2017.

2 | METHODS

Data of patients who fulfilled the diagnostic criteria of CF were included. We adhered to the ECFS Patient Registry (ECFSPR) inclusion criteria and included patients who fulfilled the diagnostic criteria: (a) two sweat tests greater than 60 mmol/L chloride, and (b) one sweat test greater than 60 mmol/L chloride and DNA analysis—two identified disease-causing CF mutations. If the sweat value was less than or equal to 60 mmol/L: (a) DNA analysis—two identified disease-causing CF mutations, and (b) clinical presentation—typical features of CF.[5] Different from the ECFSPR criteria, we could not use transepithelial nasal potential difference (NPD) because it is not routinely performed in Turkey, other than for research purposes in some centers. If DNA analysis could not be performed or if genotyping results revealed no CF causing mutation or mutations not causing CF, then the diagnosis was based on clinical presentation and sweat chloride test greater than 60 mmol/L.

Data of patients were annually recorded by each center in a software program that was specially developed for the CFRT. Demographic and annually recorded data consisted of 15 and 79 variables, respectively. In our registry, we generally adhered to ECFSPR variable definitions.[5] Pulmonary function tests (PFT) were performed using spirometry according to standard American Thoracic Society/European Respiratory Society spirometry guidelines.[6] Forced expiratory volume in the first second (FEV1) in liters and percentage (%) predicted were recorded according to results obtained from studies of healthy persons of the same age, sex, height, and racial/ethnic background.[7] The result of the best FEV1% predicted this year was recorded like with ECFSPR variables. However, different from the ECFSPR, the best height and weight in this year were included. Weight, height measurements, and body mass index (BMI) are expressed in terms of *z* scores by using reference values issued by the Centres for Disease Control.[8] In addition, we added pseudo-Bartter syndrome (PBS) in the complications, which is not found among ECFSPR variables because it is a relatively common complication in our CF population. PBS was defined as acute exacerbation of hyponatremic and hypochloremic dehydration with metabolic alkalosis without renal pathology. Whether PBS occurred before or after a diagnosis of CF or it was the reason for diagnosis was not recorded in the registry; we only recorded whether the patient had an acute exacerbation of PBS in that year regardless of the number of exacerbations.

The Registry Working Group consisted of one member from each center that contributed to the national registry, and the Registry Board consisted of seven members who were elected from among them every 4 years. At the end of the 2017 data entry, data cleaning was undertaken by the board members and statistical analysis was performed by a private company, Pleksus. Descriptive cross-sectional analysis was performed for statistical analysis. Missing data were excluded from the analysis. Program development and statistical analysis was funded by the "Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society."

The establishment of the national registry and data input were approved by local ethics committee (Hacettepe University Ethics Board, reference numbers: HEK 07/16-21 and GO 18/473-31). Informed consent was obtained from all patients/parents.

FIGURE 1 Map of centers who contributed to the national registry in 2017 and their number of patients [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

A total of 23 CF centers provided data and the total number of patients with CF registered in 2017 was 1170 (Figure 1). Among all patients, 535 (46%) were females and 635 (54%) were males. Sixty-five patients (5.5%) had meconium ileus. Among 293 patients who were under 3 years of age, 240 patients (81.9%) were diagnosed through newborn screening (NBS). The oldest patient was aged 42 years, the median age of the patients in 2017 was 7.3 years; the age distribution of patients who were alive at the end of 2017 is shown in Figure 2. The median age at diagnosis was 1.7 years; the oldest age at diagnosis was 41 years. The number of patients aged 18 years and over was 51 (4.6%). Among all patients, 15 (1.2%) patients died and 47 (4%) were lost to follow-up, thus a total of 1108 patients were alive at the end of 2017.

The results of sweat tests were reported in 1055 (90.2%) patients; among these, 271 patients had two sweat tests, and 784 patients had one sweat test. Sweat test results were not performed or unknown in 115 (9.9%) patients. The median chloride level of the first and second sweat tests of all tested patients were 90 ± 29.6 and 86.5 ± 27.4 mmol/L, respectively. The number of patients with sweat chloride more than 60 mmol/L was 757 (80.7%) and 331 (85.3%),

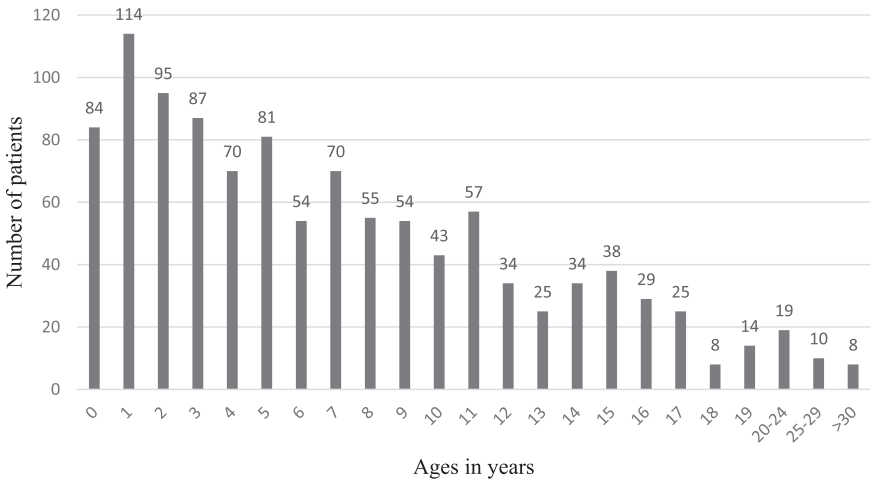

FIGURE 2 Age at follow-up of patients who were alive at the end of 2017

between 30 and 60 mmol/L it was 129 (13.8%) and 46 (11.9%), and less than 30 mmol/L was 52 (5.5%) and 11 (2.8%), in the first and second sweat tests, respectively. In patients who were not genotyped or in whom both mutations were not identified, the median chloride level in the first and second sweat tests were 93 ± 31.8 and 87 ± 27.8 mmol/L, respectively. In patients, in whom one mutation was not identified, the median chloride level in the first and second sweat tests were 92.5 ± 27.2 and 85 ± 28 mmol/L, respectively. Among 889 patients whose sweat chloride was more than 60 mmol/L in the first and/or in the second sweat test, 469 patients (52.7%) had no two CF-causing mutations or were not genotyped.

Among the available data of 1119 patients, genotyping was performed in 978 (87.4%) patients; two mutations were identified in 539 (55.1%) patients, one mutation was identified in 193 (19.7%) patients, and no mutations could be found in 246 (25.2%) patients. The prevalence of patients who were F508del homozygous was 8.8% and F508del heterozygous was 12.9%. In the tested patients, 185 different kinds of mutations were identified. Among 1271 alleles where a mutation was detected, the most common mutation was F508del only in 357 alleles (28%). The allelic frequencies of the remaining mutations were less than 1% (Table 1).

PFT results were available in 411 (71.2%) patients among 577 alive patients who could perform spirometry. The median FEV1% predicted was 90.5 ± 21.3 between ages 6 and 9 years, 89 ± 24.4 between 10 and 14 years, 82 ± 28.7 between 15 and 19 years, 56 ± 25.2 between 20 and 24 years, 63 ± 27.3 between 25 and 29 years, and 55.5 ± 16.7 between 30 and 40 years.

There were 245 (20.9%) patients with chronic *Pseudomonas aeruginosa* infection and 295 (25.2%) patients with chronic *Staphylococcus aureus* infection. In 2017, 14 (1.2%) patients had *Burkholderia cepacia* complex, and 27 (2.3%) patients had *Stenotrophomonas maltophilia*.

Median *z* scores for weight, height, and BMI are shown in Figure 3.

The most common complication was PBS in 120 (10.2%) patients. The ages of the patients with an acute exacerbation of PBS ranged between 1 month and 20 years; there were 23 patients (19.2%) younger than 12 months, 35 patients (29.2%) between 12 and 23 months, 37 patients (30.8%) between 2 and 5 years, 20 patients (16.6%) between 6 and 10 years, and 5 patients (4.2%) aged between 11 and 20 years. Their mean age was 3.7 years. Most patients (86.7%) used recombinant human DNase (rhDNase); the use of inhaled antibiotics (inhaled tobramycin and inhaled colymicin) was recorded in only 15.8% of patients, although the rate of chronic *P. aeruginosa* infection was 25.2%. Pancreatic enzyme supplements were prescribed in 87.4% of patients and oral nutritional supplements were provided to more than half of the patients (55.4%). No patients were using CFTR modulators because they are not reimbursed in Turkey yet. Taking the warm climate in our country

TABLE 1 Allelic frequencies of the 15 most common mutations and number of patients carrying these mutations

Mutation name	Number of alleles	Allelic frequency (%)	Number of patients carrying the mutation	Number of homozygote patients
F508del	357	28	256	101
N1303K	63	4.9	49	14
G542X	58	4.5	46	12
1677delTA	52	4	39	13
G85E	48	3.7	32	16
2183AA− >G	41	3.2	28	13
2789+ 5G>A	37	2.9	29	8
M470V[a]	32	2.5	23	9
E92K	30	2.3	19	11
D110H	24	1.8	14	10
W1282X	24	1.8	20	<5
D1152H[b]	21	1.6	13	8
R347P	21	1.6	16	5
L997F[a]	17	1.3	13	<5
R334W	14	1.1	13	<5

[a]M470V and L997F are non-cystic fibrosis causing variants.
[b]D1152H is a variant of varying clinical consequences according to CFTR2 website (The Clinical and Functional TRanslation of CFTR (CFTR2). Copyright 2011 U.S. CF Foundation, Johns Hopkins University, The Hospital for Sick Children. Available at http://cftr2.org).

FIGURE 3 Median *z* scores for weight, height, and body mass index by age group

TABLE 2 Prevalence of complications

Complication	Number of patients	%
Pseudo-Bartter syndrome	120	10.2
Sinusitis	110	9.4
Chronic liver disease[a]	93	7.9
Gastroesophageal reflux	47	4
CF-related diabetes	40	3.4
Osteoporosis	29	2.4
Allergic bronchopulmonary aspergillosis	19	1.6
Major hemoptysis over 250 mL	7	0.5
Pneumothorax requiring chest tube	<5	0.1
Malignancy	<5	0.1

[a]Chronic liver disease included: liver disease without cirrhosis, and cirrhosis with and without portal hypertension/hypersplenism.

and sodium losses in our patients into consideration, routine salt supplementation is recommended for all infants aged under 2 years, and specific levels of salt supplementation depending on age and condition in older children and adults.[9] The complications and treatments of the patients are shown in Tables 2 and 3, respectively.

Among 15 patients who died in 2017, 12 patients died of respiratory failure, one of liver failure, and the cause of death in two patients was unknown. The age of death ranged between 1 month and 34 years; the median age at death was 13.5 ± 9.9 years. The deceased 12 patients were aged under 18 years, thus the pediatric mortality under the age of 18 years was 80%.

TABLE 3 Treatments

Treatment	Number of patients	%
Pulmonary		
Recombinant human DNase	1015	86.7
Inhaled bronchodilator	248	21.1
Inhaled steroid	204	17.4
Inhaled antibiotics	186	15.8
Hypertonic saline	94	8
Azithromycin	74	6.3
Inhaled mannitol	59	5
Oxygen	35	2.9
Noninvasive mechanical ventilation	31	2.6
Oral steroid	13	1.1
Other		
Pancreatic enzyme	1023	87.4
Vitamin supplement	972	83
Oral nutritional supplements	649	55.4
Ursodeoxycholic acid	190	16.2
Proton pump inhibitors	141	12
Calcium	63	5.3
Insulin	25	2.1
Biphosphonates	7	0.6
Gastrostomy	5	0.4

4 | DISCUSSION

The first CF registry was started in the United States in 1966, and it was then established throughout the United States, Europe, and Oceania.[1] U.S. CF Foundation Patient Registry and ECFSPR are the most comprehensive examples of registries for patients with CF. Most CF registries were developed from national patient organizations.[1,2] Our registry was developed by the "Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society," which is the first CF society in Turkey, established in 1995 with the aim of increasing awareness of CF and training health personnel about CF care in the country. We collected demographic and annual data similar to other CF registries and worked for almost 10 years to encourage centers to provide data, facing almost all known challenges in maintaining the registry such as numerous missing and incomplete data, and lack of time for data entry. Data cleaning was undertaken by the efforts of the board members. No financial support was provided for either data-entry or data-cleaning process. Our national registry has been contributing to the ECFSPR since 2016.[5]

The establishment of the CFRT has provided the first estimates of the prevalence of CF, although the number of registered patients is considered to be much lower than the real number. There were only 1170 registered patients and we estimate that the coverage rate is 30% of the entire CF population in the country. Nonetheless, we believe that our data gives a small estimate of our CF population. The rate of consanguineous marriage in our country is very high at 23.2%[10]; therefore, the prevalence of CF, which is inherited autosomal recessively, is expected to be much higher. According to the Turkish Statistical Institute, the number of live births in Turkey was reported as 1 291 055 in 2017[10]; therefore, it is obvious that the number of patients with CF in the country should be much more. We believe that the main reason for the low number of patients with CF in the registry is lack of knowledge about CF among health providers and therefore a lack of diagnosis, especially in rural areas. Besides, there are still some CF centers that are yet to include their data due to a lack of data-entry personnel, time, and financial support, which are the greatest challenges in maintaining a patient registry. Additionally, in the ECFSPR annual report of 2017, the number of patients in Turkey was reported as 1447, which may be confusing.[11] However, this number reflects both the data of patients registered in our national CFRT and another center in Turkey that did not contribute to the CFRT and sent their patients' data directly to the ECFSPR.

NBS for CF was implemented in Turkey on January 1st, 2015, by the Ministry of Health using two repeated immunoreactive trypsinogen (IRT/IRT) tests. In our NBS policy for CF, the IRT test is obtained in the first days of life and a cut-off value over 90 μg/L is considered to be positive. Then, a second IRT test is obtained in newborns who were positive in the first IRT at the age of 7 to 14 days. At a level

above 70 μg/L, newborns are referred to a specialized center for sweat test procedures. Specimens for the IRT test are taken from every newborn baby all over the country; however, sweat tests can be conducted in only 31 out of 81 provinces in Turkey. There is only one report about patients with CF being diagnosed with NBS after the implementation of screening program from Hacettepe University, which is the largest CF center in Turkey. In this report, of the 945 patients who were admitted because of IRT/IRT positivity in this center over a 3-year period between 2015 and 2018, 30 patients were diagnosed as having CF and their mean age at diagnosis was 1.5 (range, 1-3) months.[12] Taking into consideration that the median age at diagnosis in our patients in 2017 was 1.7 years, we hope that NBS in our country will lead to earlier diagnosis and therefore improved survival of our patients.

Meconium ileus is often the earliest clinical manifestation of CF and occurs in about 15% to 20% of patients.[13] However, only 5.5% of our registered patients had meconium ileus. This low number can be explained by the lack of knowledge about CF in some parts of the country, which may lead to undiagnosed patients with CF with meconium ileus who might die at early ages.

Improvements in CF care have led to a substantial and growing adult population in developed countries; in the United States, more than half of all people with CF are aged over 18 years.[14] However, although our oldest age was 42, the median age of the patients still alive in 2017 was found to be 7.3 years, and only 4.6% of our patients were adults. CF is still managed by pediatricians in most centers in Turkey, but transition to adult clinics has just been implemented in those centers. The contribution of adult CF care providers in the registry will hopefully demonstrate the real number of adult patients with CF in our country.

Ideally, two sweat tests are performed in Turkey, but some centers did not report or did not perform the second test. In addition, in our registry, sweat chloride test results were missing in 9.9% of patients, which is a limitation of our registry. Moreover, CF genotyping cannot be performed in every center; therefore, 12.6% of our patients were not genotyped due to a lack of experienced laboratories in some regions. Among genotyped patients, two mutations were found in only half of our patients; therefore, in our country's conditions, patients who cannot be genotyped or those without two CF-causing mutations can only be diagnosed through sweat test plus typical clinical criteria of CF, because transepithelial NPD also cannot be measured routinely, which can be considered as a weakness of our registry. Accordingly, the sweat test is very important for diagnosing CF in our country and should be interpreted carefully by taking patients' clinical findings into consideration because it can have false-negative results in conditions due to technical problems mostly. These are the major challenges of our registry that need to be overcome in the future.

Although genotyping was performed in 87.4% of our patients, no mutations could be found in one-quarter of our population. In a study from Turkey, only 52.5% of disease-causing mutations were detected in patients with CF and 47.5% of CF alleles were unidentified, which reflected the high molecular heterogeneity of the Turkish population.[15] A survey study conducted among 373 European CF centers that asked which CFTR mutations had been found in Turkish and North African immigrant patients with CF revealed that 31 different mutations were reported in Turkish patients; however, 35.8% of CF alleles in Turkish patients living in Europe had not been identified.[16] In our registry, only 8.8% of patients were F508del homozygous in contrast to most European countries. Among the alleles tested, the most common allele frequency was F508del with an allelic frequency of only 28%. Other studies in Turkey revealed the allele frequency of F508del to be between 18.8% and 36.3%.[15,17-20] In our registry, the other common mutations were N1303K, G542X, 1677delTA, G85E, 2183AA− >G, and 2789+ 5G>A, which had low allele frequencies between 4.9% and 2.9%. In a recent study from another center in Turkey whose data were not included in our national registry, CFTR mutation analysis from 250 patients with CF revealed that at least two mutations were identified in 87.6%, only one mutation was detected in 7.6%, and no mutations were identified in 4.8% of patients. Their most common mutation was F508del at 28.4%, similar to our registry, followed by 1677delTA at 6.4%.[21] Another center in Turkey demonstrated that their overall allele informativity increased from 11.7% to 38.2% after whole-exon sequencing of CFTR in their 17 patients with CF in whom no mutations were identified using common mutation analysis.[22]

When we compare the median z-score for height, weight, and BMI of our patients with the 2017 ECFSPR annual report, it is obvious that all these parameters are much lower than in all other European countries. These low scores provide very strong evidence showing that we must pay attention to following up the nutritional status of our patients and give necessary nutritional support as soon as they need, which seems to be a very neglected issue in our CF care. Improving patients' nutritional care will improve their pulmonary functions, which decrease by age as expected, and hopefully increase our patients' survival. One limitation in our data collection is that, for analysing the nutritional status of our patients, we included the best height and weight in this year which are actually the last measurements in that year for children due to growth velocities, and BMI calculated with these values do not reflect the best BMI *z* scores for real. Therefore, we intend to adapt our definitions according to ECFS who analyse weight and height measured at the date of recorded FEV1 or, if no lung function, last recorded weight and height of the year.

The prevalence of chronic *P. aeruginosa* infection in our national registry was 20.9%. This percentage increases up to 22.82% when the data of other centers in Turkey is added as seen in the 2017 ECFSPR report.[11] In Europe, the rate of chronic *Pseudomonas* infection is between 14.29% and 62.16%[11] and our prevalence, which is lower than most countries' prevalence, may be contributed to by poor reporting or lack of experienced laboratories for diagnosing chronic infection in some of our centers.

Although our 20.9% of patients were chronically infected with *P. aeruginosa*, the use of inhaled antibotics was only 15%, which needs to be increased. The use of inhaled antibiotics is reimbursed in

patients who have chronic infection with *P. aeruginosa* in our country. Besides, almost all drugs including recombinant human DNase, inhaled bronchodilators, azithromycin, inhaled mannitol, noninvasive mechanical ventilation, pancreatic enzyme, and other nutritional support are reimbursed in our country for CF patients. When the treatments of our patients are compared with other countries in Europe, rhDNase is the second-highest among other European countries; however, the use of macrolides, bronchodilators, and oxygen seem to be low when compared with most countries.[11] The percentage of our patients using hypertonic saline was the lowest among European countries in 2017 because hypertonic saline began to be reimbursed in 2018.[11]

The most common complication was acute exacerbations of PBS in our 120 patients (10.2%). There are no data on the incidence of PBS as a complication of CF in Northern Europe; retrospective case series studies from Turkey, Jordan, and Saudi Arabia suggest an incidence range of 12% to 18.3% in children.[23-26] Scurati-Manzoni et al[27] reviewed patients with CF with PBS worldwide over the period of 1951 to 2013, and found reports of a total of 262 cases. The exact mechanism of PBS is not known; the high prevalence PBS in our country can be contributed to its warm weather conditions, but genetic factors may also be a factor and deserves further investigation.

Most of our patients died of respiratory failure, but it should be taken into consideration that some undiagnosed infants could have died because of meconium ileus and this can contribute to the low number of deceased patients in Turkey. None of our patients had lung or liver transplantation in 2017. Few patients undergo lung transplantation in our country and our future aim is to determine the number of patients with CF who need a lung or liver transplant, and therefore encourage surgeons to perform transplantation and hopefully increase organ donations in the country.

Finally, CFTR modulators are not yet reimbursed in Turkey because of their high cost and lack of information about the number of patients who are candidates for these drugs. Our registry will enable us to identify the number of patients who would benefit from CFTR modulators and urge health authorities to reimburse these drugs.

This report was a beginning for our country in spite of considerable challenges such as the low coverage rate, lack of genotyping, unidentified mutations, incompleteness of patient records, and especially missing data related to lung functions. Efforts to sustain our registry and increase data input with the involvement of all pediatric and adult CF centers in the country will provide more accurate data and help to improve CF care including improvement of pulmonary and nutritional status, and the survival of our patients in our country.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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