TJPD Turkish Journal of Pediatric Disease

Original Article

Clinical and laboratory findings of patients with cystic fibrosis: a single center experience from Türkiye

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ABSTRACT

Objective: The objective of this study was to evaluate the clinical characteristics of patients with cystic fibrosis (CF) and to determine whether there is a relationship between nutritional status and pulmonary functions. Additionally, the study aimed to investigate the relationship between the CFTR genotype and the occurrence of cystic fibrosis-related diabetes (CFRD), as well as the impact of CFTR mutations on the severity of CF pulmonary disease.

Material and Methods: The data of 300 CF patients were retrospectively analyzed. Clinical and laboratory characteristics were obtained from unit database. The patients' growth indices and nutritional status were assessed based on age groups.

Results: Among the 300 patients, 69.5% were diagnosed under age one year old. The earliest diagnosed patient was 2 days old, and the latest diagnosed patient was 31 years old. The most common presenting complaints were recurrent lung infections and gastrointestinal symptoms. Genotyping was performed in 241 patients (80.3%), and 16.6% of these were found to be homozygous for F508del. The allelic frequency of F508del was found to be 41.4%. Eighty-three patients (29.7%) were colonized with *Pseudomonas aeruginosa*, and they were found to have more severe lung disease compared to non-colonized patients (p=0.004). We observed that 30% of the patients with CFRD and 12.7% of the non-diabetic patients had severely impaired pulmonary function (p=0.004). The patients who had F508del mutation in at least one allel were found to have a higher risk of developing diabetes compared to those who did not have (p=0.049).

Conclusion: *Pseudomonas aeruginosa* colonisation and development of CFRD are associated with impairment in pulmonary functions in CF patients.

Keywords: Cystic fibrosis, Mutation, Pulmonary function

INTRODUCTION

Cystic fibrosis (CF) which was once considered as a childhood disease, is now recognized as a condition affecting adults as well, due to better understanding the pathophysiology of the disease, development of reliable diagnostic methods, identification of new mutations and advances in the treatment modalities. CF is an autosomal recessive metabolic disorder characterized by the dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This condition primarily affects the sweat glands, pancreas, and the mucous glands of the respiratory, gastrointestinal, and genital tracts. As a result, individuals with CF often experience chronic pulmonary infections and inflammation, pancreatic exocrine insufficiency, and male infertility (1).

In a recent study from our country the incidence of CF was found to be 2.9 per 10000 live births in Central Anatolia (2). However, since the rate of consanguineous marriage is high in our country, the prevalance of the disease is estimated to be much higher than expected.

In this study, we aimed to evaluate the clinical characterictics and laboratory findings at the time of the diagnosis and at the time of the last follow-up in patients with CF. The nutritional classifications were compared with FEV1 and *P. aeruginosa* colonization across different age groups. Additionally, we

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Received : 06.10.2024
Accepted : 27.11.2024
DOI:10.12956/tchd.1562280

aimed to identify relationship between CFTR genotype and the occurrence of cystic fibrosis-related diabetes (CFRD), and the impact of CFTR mutations on the severity of CF pulmonary disease.

MATERIALS and METHODS

In this retrospective study, data of 300 CF patients were analyzed between January 2011 and June 2012 at pediatric pulmonology unit of Hacettepe University. Among 300 patients, 278 of them had clinical visit during this period because two patients died and 20 did not apply for follow-up visits.

The patients who fulfilled the following diagnostic criteria of CF were included in the study: (a) two sweat tests greater than 60 mmol/L chloride, and (b) one sweat test greater than 60 mmol/L chloride and DNA analysis revealing two identified disease causing CF mutations. If the sweat test result is less than or equal to 60 mmol/L: (a) DNA analysis revealing two identified disease causing CF mutations, and (b) clinical presentation consistent with typical features of CF (3).

We evaluated clinical and laboratory findings of patients from the unit databases including; gender, age, complaints, symptoms, physical examination findings, height and weight measurements, presence of pancreatic insufficiency, results of genotyping, sweat chloride test, pulmonary function test. Also microbiological evaluation of the respiratory cultures, findings of the chest X-rays, abdominal ultrasonography and if available computed tomography were recorded. Patients were evaluated for the development of CF related complications.

Sweat chloride concentration was measured via the quantitative pilocarpine iontophoresis test, as described by Gibson and Cooke method (4). Genetic mutation analysis was performed using a CF gene panel that included 36 CFTR gene mutations. Pancreatic insufficiency was defined as having the classic symptoms and signs including the weight loss, gas, dyspepsia, bloating, foul-smelling oily stools and steatorrhea. Although fecal elastase is the most used test to screen pancreatic exocrine insufficiency, during the time of the study this test could not be analyzed in our hospital (5). Anemia was defined as a reduction of the hemoglobin concentration or red blood cell volume below the range of values according to age and sex (6). Elevation of liver transaminases was categorized depending on age and sex (7).

The nutritional status of the patients were evaluated according to the age groups. Weight, height measurements and body mass index (BMI) were expressed in percentiles by using reference values issued by Centers for Disease Control (8). Weight-for-height (WfH) percentiles were recorded for patients under two years of age, while BMI percentiles were noted for those aged 2 to 18 years, and BMI measurements were taken for patients over 18 years old. For the patients under two years of age, WfH percentiles under 10 was defined as inadequate nutrition, percentile between 10 and 25 as nutrition at risk, percentile between 25 and 75 as normal nutrition, and percentile over 95 was defined as obese. For the ages between 2 and 18 years of age, BMI percentiles under 10 was defined as inadequate nutrition, percentile between 10 and 25 as nutrition at risk, percentile between 25 and 75 as normal nutrition, and percentile over 95 was defined as obese. For the patients over age 18, BMI under 19 was defined as inadequate nutrition for boys and girls, BMI between 19 and 22 for girls and 19 and 23 for boys as nutrition at risk, BMI over 22 for girls and 23 for boys were defined as normal nutrition.

Pulmonary function tests were conducted using spirometry in accordance with the standard guidelines by the American Thoracic Society (ATS) and the European Respiratory Society (ERS). The Forced Expiratory Volume in the first second (FEV1) was measured in liters and expressed as a percentage (%) of the predicted value, based on reference data from healthy individuals of the same age, sex, height, and racial/ethnic background (9).

Chronic colonization by *Pseudomonas aeruginosa* or *Staphylococcus aureus* was defined as the presence of *Pseudomonas aeruginosa* or *Staphylococcus aureus* in respiratory cultures for at least 6 months, based on at least three positive cultures with at least one month intervals between them (10).

Patients were evaluated for the development of CF related complications. Pseudo_Bartter syndrome was defined as acute exacerbation with hyponatremia, hypochloremia, hypokalemia and metabolic alkalosis (11). The occurence of Allergic Bronchopulmonary Aspergillosis (ABPA) was recorded; which is a pulmonary hypersensitivity disease mediated by an allergic response due to *Aspergillus fumigatus* (12). For the diagnosis of diabetes mellitus, patients with a fasting plasma glucose ≥126 mg/dl required either a confirmatory fasting plasma glucose obtained the next day or a casual blood glucose level measured. If the repeated fasting plasma glucose was ≥126 mg/dl or if the casual glucose was ≥200 mg/dl, CFRD was diagnosed. To rule out diabetes mellitus in individuals with fasting plasma glucose <126 mg/dl and with clinical symptoms of diabetes, a standard oral glucose tolerance test (OGTT) was performed. Impaired glucose tolerance was defined as 2-hour glucose levels of 140 to 199 mg/dL on the OGTT (13).

Statistical analysis

Statistical analyses were performed using the SPSS Statistics for Windows, version 15.0 (SPSS Inc., Chicago, Ill., USA). The variables were investigated using visual (histogram) and analytical (Kolmogorov–Smirnov/ Shapiro–Wilk test) methods to determine whether or not they are normally distributed. Descriptive analyses were presented using medians, interquartile range (IQR), minimum, and maximum for the nonnormally distributed and ordinal variables, means and standard deviations for normally distributed variables. The categorical data were analysed as frequency and percentage. Chi-square test was used to compare proportions in different

groups. Mann-Whitney U and Kruskal Wallis tests were used to compare nonnormally distributed parameters. A p value of less than 0.050 was considered to show a statistically significant result.

RESULTS

A total of 300 CF patients were included in the study. Among all patients 50.3% of them were male and the rate of consanguineous marriage was 39.7%.

Clinical characteristics and laboratory findings of the patients at the time of the diagnosis

Among 300 patients, 69.5% of them were diagnosed under age one year. The earliest diagnosed patient was 2 days old, and the latest diagnosed patient was 31 years old. The median age at the diagnosis was 5 (IQR, 3-29) months. Ninety-nine of the patients were diagnosed in our hospital, 201 were referred to us with the suspected diagnosis of CF. Forty-three (14.3%) of our patients had siblings with CF.

The common presenting symptoms were recurrent lung infection, diarrhea, vomiting and Pseudo-Bartter syndrome (Table I). The evaluation of the patients' nutritional status revealed that among those under 2 years of age, 71% had a WfH measurement below the 10th percentile, 2.7% were between the 10th and 24th percentiles, and 26.3% were above the 25th percentile. In patients aged between 2 and 18 years, 45.7% were below the 10th percentile, 11.9% were between the 10th and 24th percentiles, 40.7% were above the 25th percentile, and 1.7% were classified as obese. Among patients over 18 years of age, 5 had a BMI lower than 19, while 2 had a normal BMI.

Most of the patients had anemia (40.9%) and elevated liver transaminases (40.9%). The other abnormal laboratory findings were vitamin A,E,D deficiency, metabolic alkalosis, hypoalbuminemia, electrolyte imbalance, elevated immunglobulin E, elevated hemoglobin a1c, hyperbilirubinemia and hyperglycemia. Pancreatic insufficiency was diagnosed in 94.7% of the patients. Sweat tests were performed in 287 patients. The mean sweat chloride level was 99.5±24.44 mmol/l.

Thirty-seven patients performed spirometry, the median FEV1% was 80 (IQR, 60-88). Thirty-six percent of the patients had normal chest radiograph. The most common pathological findings, in decreasing order, were bilateral hyperinflation of the lungs, infiltration, chronic changes, bronchiectasis, and atelectasis. Within one year of the diagnosis, chest tomograpy was performed to 19.7% of the patients and bronchiectasis and peribronchial thickening were the most common findings. Abdominal ultrasonography was normal in 51.5% of the patients, while hepatomegaly was detected in 18.7%.

At the time of the diagnosis *Pseudomonas aeruginosa* (n=52) and *Staphylococcus aureus* (n=54) were the most frequently isolated microorganisms in the respiratory cultures. No microorganism was isolated in 59% of the patients.

Table I: The presenting symptoms and the findings of the patients

Symptoms	Values*
Recurrent lung infection	117 (39)
Diarrhea /vomiting	95 (31.7)
Pseudo-Bartter syndrome	55 (18.3)
Failure to thrive	51 (17)
Chronic cough	44 (14.7)
Steatorrhea	35 (11.7)
Siblings of patients with CF	21 (7)
Meconium ileus	20 (6.7)
Anemia	15 (5)
Saltytaste on skin	13 (4.3)
Pretibial edema	8 (2.7)
Elevated liver transaminases	7 (2.3)
Constipation	5 (1.7)
Prolonged jaundice	5 (1.7)
Rash	4 (1.3)
Hemoptysis	3 (1)
Rectal prolapse	3 (1)
Atelectasis	2 (0.7)
Acute pancreatitis	1 (0.3)

**: n (%)*

Table II: Allelic frequencies of the 14 most common CFTR mutations

Mutation name	Allelic frequencies*
F508del	133 (41.4)
G85E	33 (10.2)
1677delTA	23 (7.1)
2789+5G-A	22 (6.8)
N1303K	18 (5.6)
2183AA-G	13 (4.0)
G542X	11 (3.4)
R334W	9 (2.8)
W1282X	9 (2.8)
CFTRdele2,3	7 (2.1)
3120+1G-A	6 (1.8)
3849+10kbC-T	6 (1.8)
621+1G-T	4 (1.2)
R347P	4 (1.2)

**: n(%)*

Genotyping was performed in 241 (80.3%) patients. Two mutations were identified in 171 (70.9%) patients and no mutations could be found in 48 (19.9%) patients. The prevalence of the patients who were F508del homozygous was 16.6% and F508del heterozygous was 22%. Among 315 allels where a mutation was detected, the most common mutation

was F508del. The other most common mutations were G85E, 1677delTA,2789+5G-A and N1303K in decreasing frequency (Table II).

Clinical characteristics and laboratory findings at the time of inclusion

Among 300 patients, 278 of them had clinical visit during this period because two patients died and 20 did not apply for follow-up visits. The median age was 7 years and 6 months (min 3 months of age, max 39 years). Sixty-seven percent of the patients had normal physical examination findings, while the most common pathological findings were crepitant rales and rhonchi.

The evaluation of the patients' nutritional status at the time of inclusion revealed that among those under 2 years of age, 9.4% were below the 10th percentile, 9.4% were between the 10th and 24th percentiles, and 81.2% were above the 25th percentile. In patients aged 2 to 18 years, 27.7% were below the 10th percentile, 11% were between the 10th and 24th percentiles, 54.8% were above the 25th percentile, and 6.5% were classified as obese. Among patients over 18 years of age, 19 had a BMI lower than 19, while 24 had a normal BMI. The mean BMI for boys and girls over 18 years was 22.2±4.59 and 21±2.82, respectively.

At the time of inclusion 128 patients performed spirometry, the median FEV1% was 76 (IQR, 59-90). Eight of the patients had FEV1 below 30%. The most common pathologic findings of chest radiograph were bronchiectasis, atelectasis and chronic changes. Chest tomography was performed in 32 patients, the most frequent pathologic findings were similar to those found in chest radiograph. Abdominal ultrasonography was normal in 43.9% of the patients, and hepatomegaly was detected in 17.7%.

P.aeruginosa (n=113) and *S. aureus* (n=136) were the most frequently isolated microorganisms in the respiratory cultures at the time of the inclusion consistent with the results at the time of diagnosis. Eighty three (29.7%) patients were colonised with *P. aeruginosa* and nine (3%) were colonised with *S. aureus*.

We observed that up to 35% of the patients developed gastrointestinal and respiratory system complications. The most common respiratory system complication was bronchiectasis, followed by ABPA, asthma, hemoptysis, atelectasis, and pneumothorax. The most frequent gastrointestinal system complications were hepatomegaly, hepatosteatosis, elevated liver transaminases, biliary disease, cirrhosis, splenomegaly and pancreatic steatosis. Endocrin complications occured in 6.7% of the patients. Ten patients had CFRD and 15 patients had impaired glucose tolerance.

The relationship between nutritional status and pulmonary function was evaluated; no statistically significant difference in FEV1% was found based on the nutritional status of patients under and over 18 years of age (p=0.170 and p=0.810, respectively). Figure 1 illustrates the relationship between nutritional status and FEV1% in patients under 18 years old. Figure 2 shows the relationship between the nutritional status and FEV1% in patients over 18 years old.

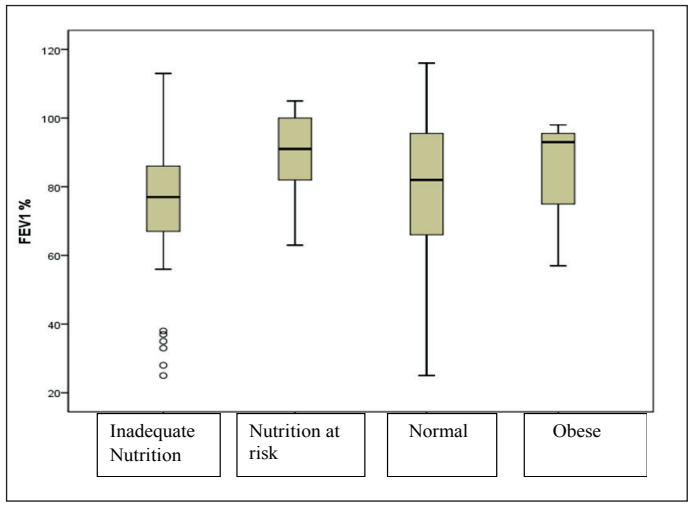

Figure 1: The relationship between the nutritional status and FEV1% of the patients. under age 18 years old.

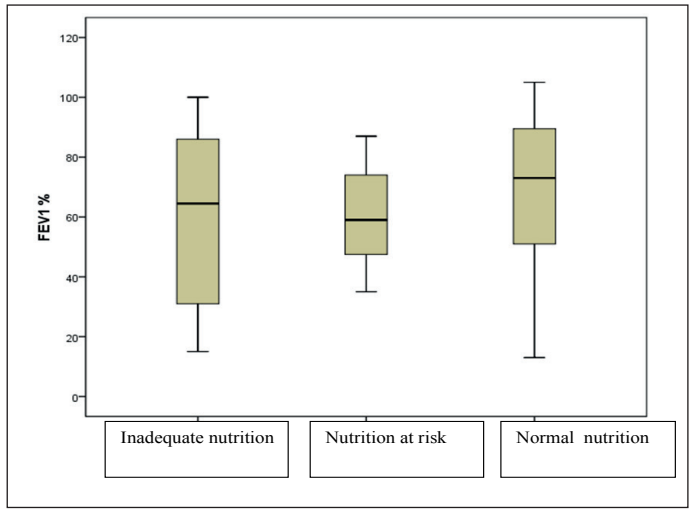

Figure 2: The relationship between the nutritional status and FEV1% of the patients over age 18 years old

The FEV1% of the patients were compared according to CFTR mutations and no statistically significant difference was found (p=0.250) (Figure 3). Twenty percent of the patients who were F508del homozygous had severely impaired pulmonary function. 5.9% of the patients who were F508del heterozygous and 9.1% of patients with F508del and unknown mutation had severely impaired pulmonary function. There was no statistically significant relationship between having F508del mutation and severity of impaired pulmonary function (p=0.360). Patients with *P. aeruginosa* colonization exhibited more severely impaired pulmonary function (p=0.004). The median FEV1% of the *P. aeruginosa* colonized patients was found to be statistically lower than non-colonized group (p=0.001).

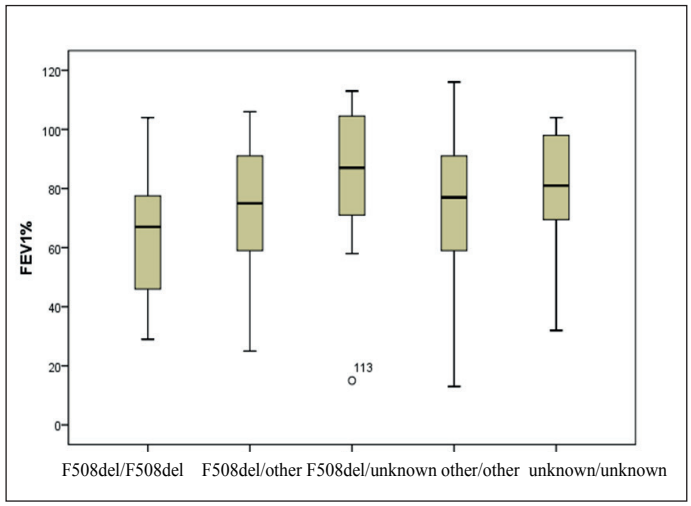

Figure 3: The relationship between FEV1% and type of the CFTR mutations

The relationship between nutritional status and *P. aeruginosa* colonization was evaluated according to the age groups and no statistically significant difference was found between the colonized and non-colonized groups (p=0.670, p=0.720 and p=0.980, respectively). There was no statistically significant difference in *P.aeruginosa* colonization between those with and without F508del mutation (p=0.440). Also no statistically significant difference was found in the severity of the lung disease according to median FEV1% in patients with and without MRSA in the respiratory cultures taken at the time of the inclusion (p=0.300).

We observed that 30% of the patients with CFRD and 12.7% of the non-diabetic patients had severely impaired pulmonary function according to FEV1% values (p=0.004). The patients who had F508del mutation in at least one allel were found to have higher rate of developing diabetes compared to those who did not have (p=0.049).

DISCUSSION

In this study clinical and laboratory findings of 300 patients were examined in our unit which is the largest CF center in Türkiye. Forty-three (14.3%) of our patients had siblings with CF. Our results were consistent with the Cystic Fibrosis Foundation annual report of 2023 that 13.9% of their patients had a family history of CF (14). Recently, a multicenter study from our country which evaluated 1170 CF patients, revealed that the median age at diagnosis was 1.7 years and 240 patients were diagnosed through newborn screening (15). In our study we found that most of our patients (69.5%) were diagnosed within the first year of life and median age at diagnosis was 5 months. According to the data of Cystic Fibrosis Foundation annual report of 2018 and European Cystic Fibrosis Society Patient Registry (ECFSPR) annual report of 2017, median age at the diagnosis was 3 and 4 months, respectively (16,17). It is a pleasure to see that most of the patients in our country are diagnosed at an early age.

Cystic Fibrosis Foundation reported that 54.1% of all new diagnoses and 85.1% of diagnoses among those less than 6 months old were as detected by newborn screening in 2023 (14). Doğru et al. (15) showed that among 293 patients who were under 3 years of age, 81.9% of them were diagnosed via newborn screening. At the time of our study newborn screening for CF was not implemented in our country's national screening programme. Thus our patients were diagnosed upon the presentation of symptoms. We anticipate that the implementation of newborn screening for CF in our country will facilitate earlier diagnoses, leading to improved survival outcomes for patients.

Malnutrition in CF patients is associated with deterioration of pulmonary function; as a result it is essential to assess nutritional status in all CF patients regularly (18). Cystic Fibrosis Foundation recommends that CF patients growth percentile should be within the 50th. percentile according to their age group. When BMI was compared with FEV1%, there was a correlation between improved BMI percentiles and pulmonary function in individuals aged 6 to 20 years and adults (16). Kilinc et al. (18) grouped 143 CF patients according to nutritional status and compared them in terms of pulmonary function test results, lung infections, and the hospitalization rate. Patients in the well-nourished group had significantly higher pulmonary function test results and bacterial lung infections differed significantly between groups.

Ashkenazi et al. (19) investigated the long-term correlations between nutritional status at 10 years of age and pulmonary function as well as the severity of lung disease in adulthood. Their findings indicated that a BMI z-score of less than -0.75 at age 10 was associated with a higher rate of lung transplantation in adults (19). In our study we could not find any association between the nutritional status and pulmonary function. This may be due to factors that may affect pulmonary function tests like age at diagnosis, type of the mutations, sociocultural level of family, treatment compliance and *P. aeruginosa* colonisation.

Genotyping was performed in 80.3% of our patients and 16.6% of them were F508del homozygous and allelic frequency of F508del was 41.4%. Doğru et al. (15), found that in their registry, 8.8% of the patients were F508del homozygous and 12.9% were F508del heterozygous and the allellic frequency of this mutation was 28%. In United States and Europe most of the patients had identified mutations, however, in our study no CFTR mutations were detected nearly in 20% of our patients, in consistence with the results of a recent study in our country (15-17). This can be due to the genetic heterogenity because of the high prevelance of consanguineous marriage in our country and the limited number of the mutations investigated with CF gene panel during the study period. As the CFTR modulators have been developed for specific gene mutations, identification

of the CFTR genotypes is of crucial importance to determine the patients eligibility for these drugs (20).

P. aeruginosa colonization has been shown to be associated with impaired pulmonary function and a major predictor of morbidity and mortality during both children and adults (21). According to the national CF registry in Türkiye, the prevalence of *P. aeruginosa* colonization was found to be 20.9% (15). *P. aeruginosa* was colonised in 29.7% of our patients and they had more severely impaired pulmonary function than non-colonized group. Mésinèle et al. (10), found that the decline in pulmonary function varied with *P. aeruginosa* status. The mean annual decrease in FEV1% was 0.38% per year before the initial acquisition of *P. aeruginosa*, which increased to 0.93% after its initial acquisition, and reached 1.50% per year in patients with chronic *P. aeruginosa* colonization (10). Since chronic inflammation and progressive lung injury are the major causes of morbidity and mortality in these patients, eradicating *P.aeruginosa* from the respiratory tract before the occurence of irreversible lung injury is crucial.

Life expectancy increases in CF patients in the last 60 years. However, this improvement in survival has led to patients experiencing complications in addition to lung disease and impaired nutrition. The most common of these is CFRD, which affects 40–50% of CF adults. Female sex, advanced age, reduced lung function, liver disease, steroid treatment, a family history of type 2 diabetes, and genetic factors, such as mutations in the CFTR gene and other modifier genes are known risk factors for CFRD (22). Genotypes that lead to severe CFTR dysfunction and pancreatic exocrine insufficiency are associated with an increased risk of developing diabetes over time. Individuals with severe CFTR mutations, such as F508del homozygotes, have had a risk of developing diabetes that exceeds 80% by age 50 and approaches 100% by age 60 (23). Consistent with the literature, in our study patients who had F508del mutation in at least one allel were found to have a higher risk of developing diabetes compared to those who did not have (p=0.049). It is shown that in the years preceding therapy for CFRD, reductions in pulmonary functions and BMI are observed (24). In our study FEV1% of patients with CFRD were compared with the patients who had no diabetes and it was found that 30% of the patients with CFRD and 12.7% of the non-diabetic patients had severely impaired pulmonary function (p=0.004). According the data from the adult CF patients from Türkiye, lower BMI and lower FEV1% were observed in CFRD group (21). These results indicate that CFRD adds to difficulties in maintaining nutritional status and pulmonary function in CF patients. Therefore annual screening with an OGTT is recommended for patients starting at age ten (25).

The major limitation of our study is its retrospective nature and the fact that it was conducted in the single center. Although genotyping performed in most of the patients, we were unable to identify the CFTR mutation in approximately one-fifth of the patients due to limited number of mutations screened during the study period.

In conclusion, CF is a significant disease that affects not only children but increasingly impacts adults as well. The study findings highlight the importance of CFRD that is associated with decline in pulmonary functions and minimizing *P. aeruginosa* colonization in CF patients.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the local ethics committee (Hacettepe University Ethics Board, date: 17.04.2007, reference number: HEK 07/16-21).

Contribution of the authors

Köse Çetinkaya A: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Doğru D:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Cinel G:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***Yalçın E:*** Planning methodology to reach the conclusions,Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***Özçelik U:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Reviewing the article before submission scientifically besides spelling and grammar. ***Kiper N:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Reviewing the article before submission scientifically besides spelling and grammar. ***Özen H:*** Planning methodology to reach the conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***Alikaşifoğlu A:*** Planning methodology to reach the conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in

logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***Şener B:*** Planning methodology to reach the conclusions, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***Dayangaç Erden D:*** Planning methodology to reach the conclusions, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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