

First Cystic Fibrosis Patient Registry Annual Data Report-Cystic Fibrosis Foundation of Iran

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Abstract- Cystic fibrosis (CF), as a fatal genetic condition, is associated with high morbidity and mortality rates. In Iran, limited studies exist on this disease. This study aimed to compare the demographic, clinical and paraclinical data of CF patients. This cross-sectional study was conducted in 2014-2015 on 174 CF patients referred to the Tehran Children Medical Center hospital, which is the main referral center for CF. For each patient, the forced expiratory volume in one second (FEV1) was measured, and the comparative demographic, clinical, and laboratory data of patients were recorded. Overall, 59% of studied patients were boys (n=102) and 41% were girls (n=72). The mean patient age (and standard deviations) was 7.1±5.7 years, with a range of 10 days to 28 years. In 67% of cases, the disease was diagnosed before their first birthday. The patients in this study were classified based on the FEV1 into mild (62%), moderate (33%) and severe (5%), indicating the degree of pulmonary complications. Cultures of respiratory secretions were positive for *Pseudomonas aeruginosa* and *Staphylococcus aureus*, in 23% and 16% of cases, respectively. In total, 61% of patients (n=83) were assigned to receive oral azithromycin for prophylaxis. Gastroesophageal reflux (reflux) was the most common gastrointestinal complication (35%). Regarding the complex nature of CF and the necessity of constant monitoring of patients during the life-span, the comparative demographic, clinical and laboratory analysis of patients and registering and standardization of patients' data can be a major step in the better understanding of the disease, and thereby increasing the quality of life and life expectancy in the affected population.

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Introduction

Cystic fibrosis (CF) is the most common fatal multisystem genetic disorder inherited in an autosomal recessive pattern that affects children and young adults. The prevalence of CF varies considerably among various populations around the world, with an incidence of about 1 in every 2,500 babies and carrier state frequency approximately 1 in every 25 (1). In CF patients, dysfunction of the CF transmembrane conductance regulator (CFTR) protein results in mucous hyper-

concentration and hyperproduction in the airways and organs such as pancreas, liver and intestines and causes a wide range of symptoms and complications (2-4). Classical CF is characterized by manifestations of respiratory and gastrointestinal (GI) symptoms in the first few months of life (5). However, the clinical manifestations of the disease are different even in patients with the same gene mutation (6). Chronic obstructive pulmonary disease (COPD), bronchiectasis and frequent respiratory infections are the most important cause of death in CF (7), especially in children (8). In addition, CF

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is the main cause of the most cases of exocrine pancreatic insufficiency (EPI) and pancreatic inflammation in early life (9), sodium chloride deficiency (10), chronic rhinosinusitis and nasal polyps (11), rectal prolapsed (12), the formation of gallstone (13), and insulin-dependent hyperglycemia (14). On the other hand, CF may be revealed as growth failure and occasionally causes cirrhosis and other forms of liver disorders (3,15). Therefore, the disease comes up in the differential diagnosis of many pediatric diseases. In recent years, medical advances in the treatment of CF have aimed to improve both the quality of life and management of this disease and have been led to an increase in life expectancy in these patients (11). These treatments include the use of inhaled respiratory drugs, treatment of associated illnesses, genetic counseling, dietary supplements, neonatal screening, antibiotic therapy and lung transplantation, and in recent years, treatment with Ivacaftor for patients with G551D mutation and twenty additional mutations has been approved by the US Food and Drug Administration (16,17).

There are limited studies regarding the prevalence of CF in Iran. A study by Modarresi *et al.*, about a group of high-risk children to CF indicated that the prevalence of CF disease in Iran is more prevalent than previously thought (18). However, there is still no standard patient registration system for recording the health status, treatments, and follow-ups of patients in Iran. This study aimed, for the first time, to describe the demographic and clinical data from a cohort of Iranian CF patients, to compare these data to other CF registries around the world, and to begin the process of creating an Iranian CF registry that can aid in providing evidence-based care to Iranian children and adults with CF.

Materials and Methods

Patients

This cross-sectional study was conducted from March 2014 to March 2015 in the Children's Medical Center affiliated to Tehran University of Medical Sciences, which is the main referral center in Iran. All patients who had criteria for the diagnosis of CF were included in the study. The criteria for the diagnosis of CF were based on the definition of CF in "European Cystic Fibrosis Society" (ECFS) and American Cystic Fibrosis foundation (CFF) (4,19).

Exclusion criteria were a failure to the diagnosis of CF during the study. The study was approved by the ethics committee of Tehran University of Medical Sciences. Informed consent was obtained from all adult patients or

their parents.

Methods

A detailed questionnaire was completed by interview. Patients were visited by a Pediatric pulmonary fellowship physician, and a detailed questionnaire was completed for demographic, clinical and laboratory data. The data included gender, age, birthplace, the age of diagnosis, body mass index (BMI), clinical manifestations, associated illnesses (such as pancreas insufficiency, diabetes, etc.), sweat chloride levels, taking a pancreatic enzyme supplement, use of inhaled drugs, microorganisms in respiratory secretion, and spirometry. Secretion from patients who were unable to expectorate the sputum was collected with a swab at baseline when clinically stable and at three monthly clinic visits and were cultured in the standard culture medium for bacteria to the diagnosis of aerobic bacteria. Spirometry tests were performed every 6 months for patients over 6 years of age according to the American Thoracic Society standards (20). The culture of respiratory secretions was performed every three months.

Pulmonary function test (PFT)

Spirometry tests were performed every 6 months for patients according to the American Thoracic Society standards. Spirometric measurements included forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1). Results were described as the percentage of the predicted values based on reference values of pulmonary function test (PFT). Patients were divided into five groups including those with FEV1; <30%, FEV1; 30%-49%, FEV1; 50%-69%, 70%-89% and FEV1; >90% based on FEV1 results.

Statistical analysis

Values were expressed as frequency (number and percentage), mean±standard deviation and median (interquartile range, IQR), as appropriate. Statistical analyses were performed using the software package SPSS, version (version 21.0, IBM, USA).

Results

A total of 174 patients with CF were enrolled in this study. Demographic, clinical and laboratory features of patients are presented in table 1. One hundred two (59%) patients were male, and 72 (41%) patients were female. The mean age of the patients was 7.1 years (SD, 5.7; range, 10 days to 28 years) and the mean age of CF

diagnosis was 5.4 ± 3 month. Overall, in 67% of the patients ($n=117$), the disease was diagnosed before the age of one. However 33% (57 patients) of these patients were over one-year-old when they got their diagnosis, with the maximum age of being 25-year-old. The total number of first degree relative parents was 30 (17%). Seventy-two (41%) of patients were from Tehran, and the rest were from other regions of Iran. One hundred thirty-

one (75%) of patients had Pancreatic insufficiency requiring enzymes. Seventy-nine percent of patients over six-year-old ($n=46$) had at least one pulmonary function test results. At least one respiratory secretion culture result was available for 99% of patients. Fifty-three (30%) of patients had one visit, and 121 (70%) of patients had more than one visit.

Table 1. Demographic, clinical and laboratory findings in study participants

Characteristics	Frequency	Percent
Gender	Total number of patients	174
	Boy	59
	Girl	41
Age	Mean (standard deviation)	1.7(1.4- 12.8)
	Age range	10 day- 28 year
	Patients over 18 years old	9
Age of diagnosis	Mean (\pm standard deviation)	4.5 ± 3
	Range	From birth to 25 years of age
	Under one year of age	117
	Above one year of age	57
Familial relationship of parents	First degree relatives	30
Pancreatic insufficiency	Yes	131
Pancreatic enzyme consumption	yes	131

The results of respiratory secretion cultures and respiratory drug use in patients are presented in Figure 1. The last results of respiratory secretion cultures were positive in 173 patients (99.4%), and 23% of patients were positive for *Pseudomonas aeruginosa*. Eighty-three

(61%) of patients were assigned to receive oral azithromycin, and 49 patients (36%) were assigned to receive amikacin. Only 2% of patients were assigned to receive inhalational Dornase alfa.

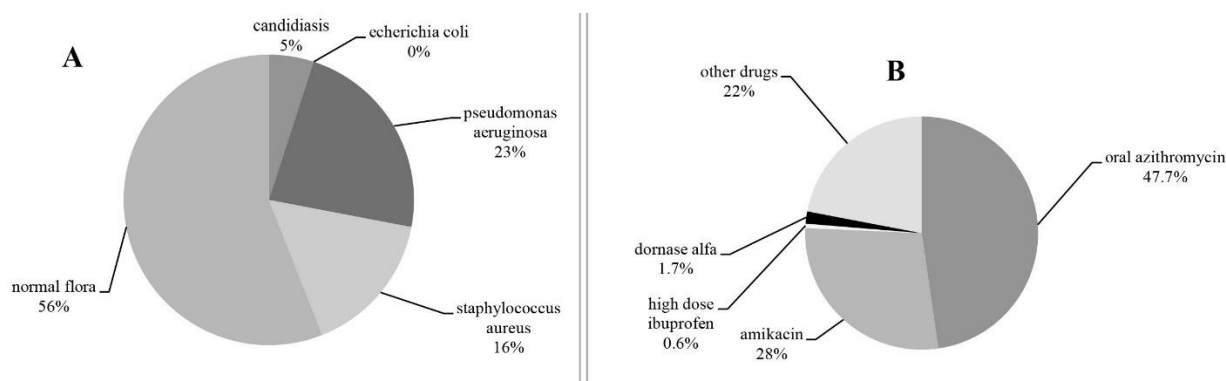


Figure 1. (A); respiratory secretions cultures and (B); consuming drugs in CF patients

Figure 2 shows the percentage of CF diagnosis based on age groups. Accordingly, the 1 to 5 months age range showed the highest age of diagnosis (84 cases). New cases of diagnosis in this age range were 9 cases. The minimum number of diagnosed patients was in the age range of 25 to 36 months ($n=7$). The age distribution of

CF patients has been shown in figure 3. In our study, the highest and the lowest percentages of patients were between 1-5-year-old and over the 20-year-old, respectively.

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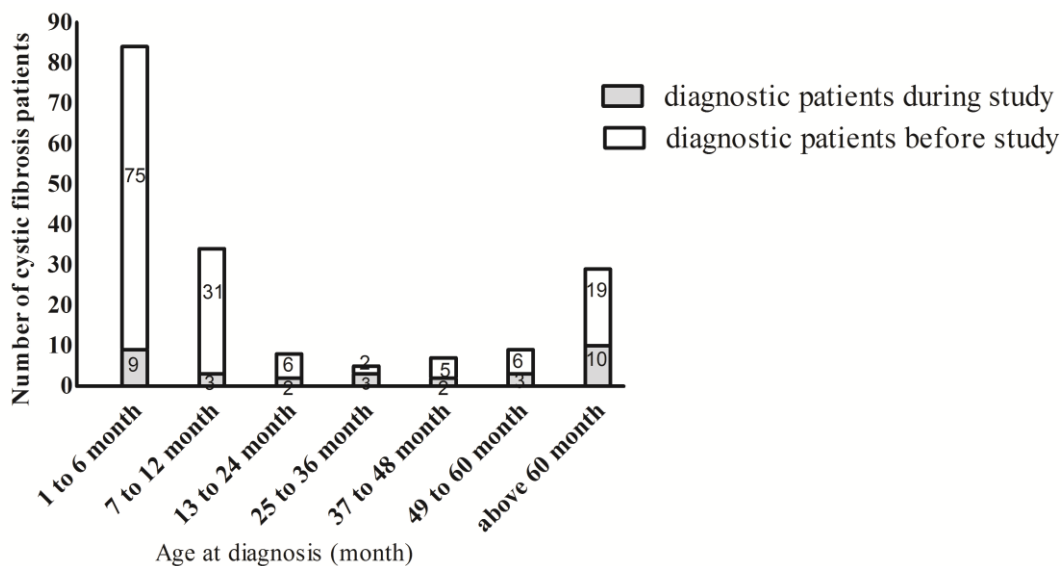


Figure 2. The frequency of diagnosed cases by age before and during the study

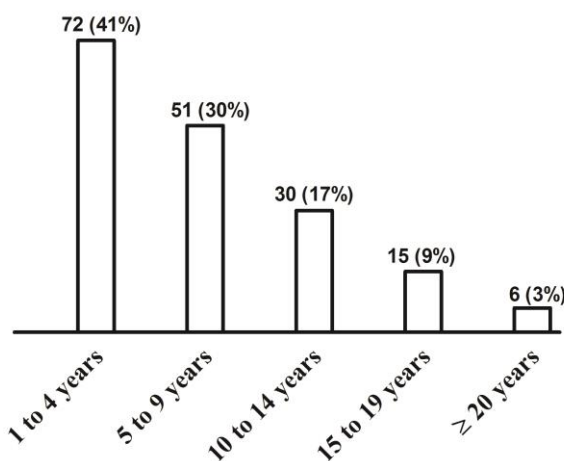


Figure 3. Distribution of age of CF patients

The results demonstrated an age-related decline in forced expiratory volume in 1 second (FEV1) (Figure 4). The age groups of patients were classified based on the FEV1 into mild (62%), moderate (33%) and severe (5%), indicating the degree of pulmonary complications (Figure 5). The analysis of BMI based on four age groups indicated an age-related decline in BMI (Figure 6).

Genetic analysis of the CFTR gene in 4 patients (2%) revealed 2 patients with F508del mutations, one with 3120+1G insertion mutation, and one patient without

detectable mutations (Figure 7).

Table 2 shows the frequencies of the most common complications in CF patients. Gastroesophageal reflux (reflux) was the most common gastrointestinal complication (35%), followed by osteopenia (22%) and nasal polyps (13%) in the population under study.

Meanwhile, the results of liver enzymes (AST and ALT) analysis were available for 124 patients, of which 21 patients (12%) were diagnosed with liver disease, including 4 cases (2%) with severe involvement.

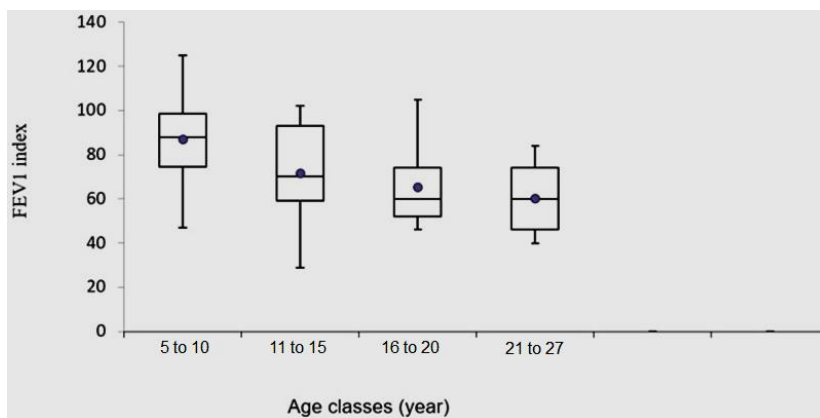


Figure 4. Dispersion indexes of FEV1 based on age categories in CF patients over 5 years old

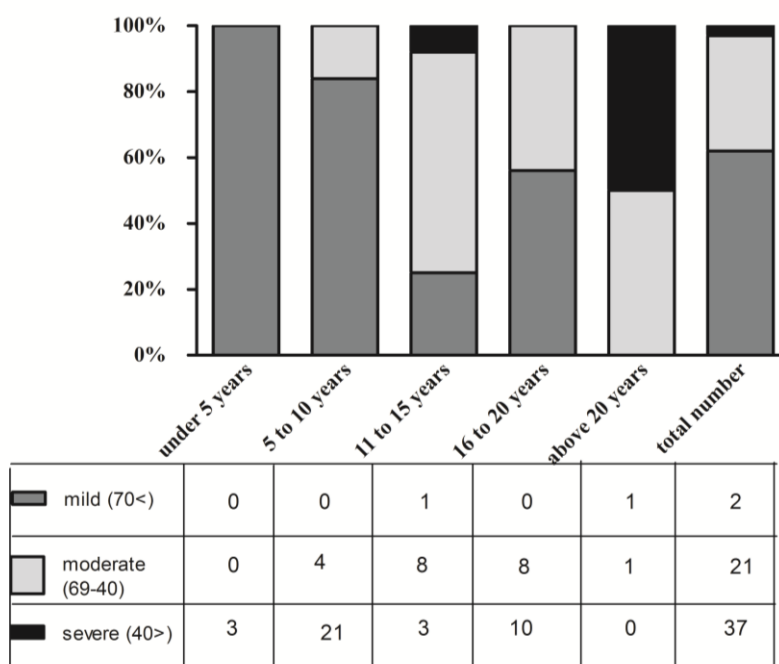


Figure 5. Frequency and percentage of FEV1 in three states of mild, moderate and severe involvement based on age groups in CF patients



Figure 6. Percentile of BMI based on different age groups in CF patient

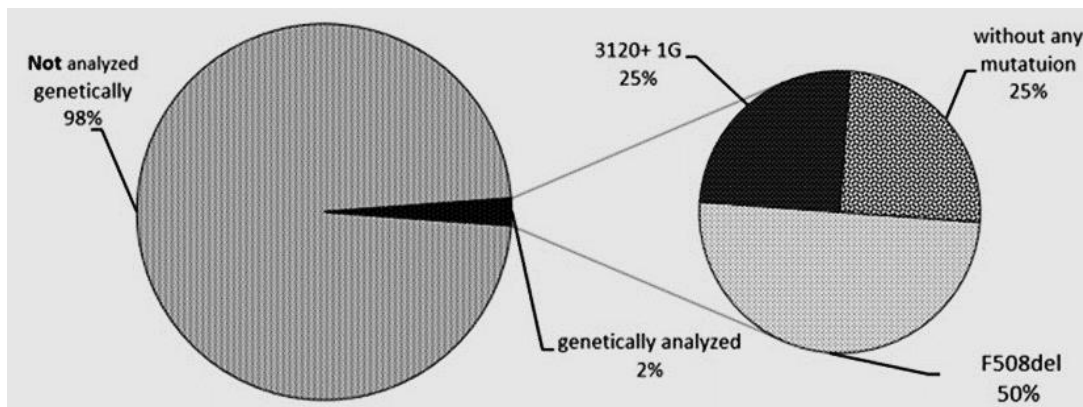


Figure 7. The frequency of genetic analysis and observed mutations in CF patients

Table 2. The frequency of some common complications in CF patients

Complication	Frequency	Percent
Gastro-esophageal reflux disease (GERD)	35	20
Osteopenia	22	13
Nasal polyp	13	7
CF related diabetes (CFRD)	8	5
Asthma	5	3
Distal intestinal obstructive syndrome (DIOS)	4	2
Sinus involvement	3	2
Allergic bronchopulmonary aspergillosis (ABPA)	3	2

Discussion

For the first time, we successfully described and compared clinical and demographic information for a number of Iranian CF patients followed at a large CF referral Center in Iran. Due to the lack of screening of infants for CF in Iran, improving the survival of patients and planning for the future seems to be the most useful activity. The results of our study may provide a useful guide for health policies and standards of care for CF patients. Clinical and laboratory studies of patients with CF are performed annually by many organizations around the world such as the CF Foundation (21). This information enables appropriate actions by health care institutions and government agencies and provides prospects for clinical and laboratory research on CF.

According to the current study of 174 CF patients, the sex distribution of CF disease appears to be approximately the same in both sexes. In accordance with our results, Marson *et al.*, who examined the demographic characteristics of CF patients did not notice any significant difference in the sex distribution of the disease (22).

The mean age of CF patients in this study was 7.1

years (SD, 5.7); while based on the 2015 statement of CF foundation, this figure was 20.9 years, and the patients over 18-year-old were 51.6% of total patients. It seems that the mean age of CF patients appears to have increased from 2000 (38.7%) to 2015. According to the 2013 European CF society report, the average age of patients with CF in 27 European countries was 18.4 years, and the patients over 18 years old were 50.9% of total (23). While in our study, the people with CF patients over 18-year-old were only 5.5%. However, in 67% of cases, the disease has been diagnosed before the age of one, that is consistent with the annual report of the CF Foundation in 2015 (66.8%) (24). In another study that analyzed clinical and genetic features of CF patients in Southwestern Iran, the authors reported a 1 to the 2-year delay between the first clinical presentation and the diagnosis of CF and concluded that delayed diagnosis has resulted in progressive disease and irreversible changes (25). The differences between the study setting and the time of study of CF patients from Southwestern Iran and our study may explain the different results obtained from these two studies.

Survival rates in CF patients can be related to the diagnosis age and beginning of treatment. In other words,

the early diagnosis of the disease can improve clinical outcomes in these patients (3). Based on the analysis of data, it seems that the diagnosis age in Iran is somewhat satisfied. However, the significant difference in survival ages compared with the European and American CF patients reflects the fact that the diagnostic, therapeutic and educational aspects of this disease in Iran are still far apart from the developed countries. Failure to follow the treatment process or other issues such as high costs of treatment, inaccessibility to specialist clinics and etc. has reduced the life expectancy of these patients in Iran, compared to the developed countries. The findings of previous studies have indicated that the reduction of FEV1 is one of the predictors of mortality in patients with CF (26). The decreasing trend of FEV1 with age was clearly visible in this study. The reduction of the FEV1 has been clearly proven in many studies in patients with CF (26-28).

The proportion of 18-years-old CF patients with normal/ mild grades ($FEV1 \geq 70$) have increased from 39.9% in 1990 to 72.1% in 2015, while this ratio for severe grades ($FEV1 < 40$) patients, have decreased from 29.9 in 1990 to 3.5% in 2015 (24). The patients in this study were classified based on the FEV1 into mild (62%), moderate (33%) and severe (5%), indicating the degree of pulmonary complications. Regarding the fact that FEV1 decreases with age, and the difference between the average age of the population in the United States (20.9 years) and Iran (7.1 years), the low percent of severe involvement ($FEV1 < 40$) in Iran (3%) cannot be compared to the value provided by the American CF Foundation (3.5%). However, it seems that due to the low average age in Iran, this level of severe involvement is high and therefore the need for more attention to FEV1, which is considered the most important mortality indicator in these patients, is necessary because therapeutic interventions can be effective in reducing this value (29).

It has been shown that low BMI is associated with low pulmonary function in patients with CF (30). Williams *et al.*, (2010) showed a positive correlation between the fat mass index and FEV1 in patients with CF (31). Therefore, proper nutrition in these patients can lead to improving pulmonary function and thereby increasing life expectancy.

Based on the respiratory secretion culture results, *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Staphylococcus aureus* (*S. aureus*) were positive in 23% and 16% of patients, respectively. *P. aeruginosa* is the most common pathogen in CF patients. *P. aeruginosa* comprises various strains and can produce a wide range

of infections that may lead to adverse health consequences (32). However, based on 2015 CF foundation report, the most common positive microbial cultures in CF patients were *S. aureus* (70.6%) followed by *P. aeruginosa* (47.5%) (24). According to the CF Foundation report, there has been a decreasing trend in the *P. aeruginosa* infection from 1995 to 2015 in CF patients, indicating an increase in effective care and treatment in these patients. However, our study showed that *P. aeruginosa* infection is more prevalent than *S. aureus* infection in Iranian CF patients under study. A recent systematic review which analyzed Sinus bacteriology in 1823 patients with CF or primary ciliary dyskinesia from 16 countries showed that *S. aureus* is found in 30% of the noses and sinuses of CF patients. Other common bacteria found included *P. aeruginosa*, coagulase-negative staphylococci, and *Haemophilus influenzae* (33).

Forty-eight percent of CF patients were assigned to receive oral azithromycin in this study. While, according to the CF Foundation report, the use of azithromycin in patients over 6-year-old was 66.6% in 2015, with a decline in its prescription since 2010 (24). The low percentage of azithromycin administration in Iranian CF patients can be due to the low average age of patients because the use of azithromycin in older age groups is more common. However, the use of inhaled drugs in recent years has shown an increasing trend (34). According to the CF Foundation report, more than 85% of patients in the year 2015 used Dornase alfa (24), while the percentage of using this drug in our study was low. In a study of Epidemiologic Registry of CF (ERCF) in the UK that was published in 2003, the effectiveness of using this drug was analyzed. The study concluded that younger patients benefit from this treatment more than older patients (35).

Therefore, it is necessary to consider dornase alfa along with other therapies in CF patients in Iran. Pancreatic insufficiency is the most common gastrointestinal complication in these patients. In our study, 75% of patients with CF demonstrated pancreatic insufficiency. It has been previously shown that pancreatic insufficiency can affect the life expectancy of 85% of these patients (36).

Management of secondary complications in CF is important for maintaining patient's health and quality of life. Esophageal reflux disease was observed in 20% of patients with CF. According to the CF Foundation report; it was about 36.3% in 2015. Osteopenia in CF patients was 13% in our study, which is somewhat similar to the CF foundation report in 2015 (11.9 %) (24).

CF-related diabetes mellitus is another common complication in these patients. The results showed that about 8% of patients with CF had this complication. According to the CF Foundation report in 2015, about 21% of patients had this problem. The low prevalence of CF-related diabetes mellitus in this study can be due to the low average age of patients because this is more common in older ages. According to the 2015 CF Foundation report, the prevalence of this complication was higher (34.9%) in ages over 18. Based on our results, in 3% of patients with CF, asthma was found that has a lower prevalence in comparison to the 2015 CF Foundation report (30.8%) (24).

The main limitations of this study were the lack of genotyping, lack of prenatal screening programs and inaccessibility of appropriate culture media for the growth of atypical bacteria. However, our study was the first study that collected CF patients' data in Iran, in which the patient visited by a multidisciplinary team. Therefore, our study can act as a basis for starting CF registry in Iran that can aid in providing evidence-based care to Iranian children and adults with CF.

Regarding the complex nature of CF and the necessity of constant monitoring of patients during the life-span, the demographic, clinical and laboratory analysis of patients and registering and standardization of patients' data, can be a major step in the better understanding of the disease, and thereby increasing the quality of life and life expectancy in the affected population.

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