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Demographic, clinical, and microbiological characteristics of cystic fibrosis patients at a referral center in southeastern Iran (2021–2024): a retrospective cross-sectional study

Azimeh Beigzadeh[1] · Fatemeh Doost-Mohammadi[2] · Maryam Gholami-Shahrebabak[3] · Reza Derakhshan[4] · Azam Gholami-Shahrebabak[3]

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Abstract

Background Cystic fibrosis (CF) is an autosomal recessive disorder leading to progressive pulmonary disease and multi-organ complications. Regional differences in clinical and microbiological profiles necessitate local characterization to optimize care. We aimed to describe the demographic, clinical, nutritional, cardiac, and microbiological features of CF patients attending Afzalipour Hospital, Kerman, Iran.

Methods In this retrospective cross-sectional study, all patients with confirmed CF (positive sweat chloride > 60 mEq/L and/or pathogenic *CFTR* mutations) who attended the pediatric clinic between March 2021 and March 2024 were enrolled. Data on demographics, sweat test, growth, chest CT, echocardiography, respiratory cultures, and metabolic complications were extracted from medical records.

Results Of 69 patients, 40 (58.0%) were male. The mean age at diagnosis was 44.41 ± 27.13 months (median: 14.0 months; IQR: 4.0–48.0 months), indicating a relatively late age at diagnosis in this cohort. Mean sweat chloride was 94.04 ± 29.80 mEq/L. Clinically documented failure to thrive (FTT) was present in 53 patients (76.8%). Among age-eligible patients, standardized anthropometric z-scores indicated moderate-to-severe undernutrition: weight-for-age Z-score (WAZ) was − 2.31 ± 0.89 (n = 14), height-for-age Z-score (HAZ) was − 1.42 ± 1.21 (n = 41), and BMI-for-age Z-score (BMIZ) was − 2.18 ± 0.94 (n = 41). Among patients aged ≥ 20 years, mean BMI was 17.1 ± 5.6 kg/m^2 (n = 11). Chest CT showed pulmonary complications in 36 (52.2%), predominantly bronchiectasis in 35 (50.7%). Elevated systolic pulmonary artery pressure (SPAP) was noted in 5 (7.2%), and left ventricular dysfunction in 10 (14.5%). Respiratory cultures were positive in 55.1%; Pseudomonas aeruginosa (43.5%) and Staphylococcus aureus (27.5%) were the most common isolates. CF-related diabetes and liver cirrhosis each occurred in 2 patients (2.9%).

Conclusions This cohort exhibits substantial pulmonary and nutritional morbidity, marked by frequent bronchiectasis, growth failure, and colonization with classic CF pathogens despite a relatively young median age.

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Late diagnosis and limited molecular characterization underline the need for enhanced diagnostic strategies and multidisciplinary care.

Keywords Cystic fibrosis · Bronchiectasis · *Pseudomonas aeruginosa* · Failure to thrive · Iran · Epidemiology · Microbiology

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes a chloride channel expressed in epithelial cells of the respiratory, gastrointestinal, hepatobiliary, and reproductive tracts [1, 2]. Defective CFTR function disrupts ion and water transport, resulting in dehydrated, viscous secretions that obstruct ducts and airways, provoke chronic inflammation, and foster polymicrobial colonization [3]. While the disease was once considered a pediatric lethal condition, advances in nutrition, antibiotics, and mucolytic therapies have extended the median survival beyond 50 years in high-income countries [4, 5].

The global epidemiology of CF reveals marked geographic and ethnic variation. In populations of Northern European ancestry, the incidence is approximately 1 in 2500–3500 live births, whereas in Middle Eastern and Asian populations the reported incidence is substantially lower, often attributed to underdiagnosis [6, 7]. The CFTR mutation spectrum has been reported to differ across regions. Previous Iranian studies suggest that the ΔF508 deletion accounts for only 15–25% of identified mutant alleles, although comprehensive national genotype data remain limited [8, 9]. In Iran, a national minimal dataset for CF registration has been proposed, but limited epidemiological data and the absence of universal newborn screening contribute to delayed diagnosis and underestimation of the disease burden [10, 11].

Chronic endobronchial infection is the primary driver of pulmonary morbidity. The airways of young children with CF are initially colonized by *Staphylococcus aureus* and *Haemophilus influenzae*, with a shift toward gram-negative opportunistic pathogens—most importantly *Pseudomonas aeruginosa*—as the disease progresses [12]. *P. aeruginosa* chronic infection accelerates the decline in lung function and is strongly associated with the development of bronchiectasis, respiratory failure, and pulmonary hypertension [13]. In addition to bacteria, fungi such as *Aspergillus* species and nontuberculous mycobacteria (NTM) are increasingly recognized as important contributors to respiratory deterioration [14].

Extrapulmonary complications, including exocrine pancreatic insufficiency (present in approximately 85% of patients), CF-related diabetes (CFRD), hepatobiliary disease, and malnutrition, are common and profoundly influence quality of life and survival [15, 16]. Moreover, with increasing longevity, cardiovascular manifestations—particularly pulmonary hypertension and subclinical ventricular dysfunction—have emerged as late-stage comorbidities [17]. Despite the growing recognition of these systemic complications, region-specific data from Iran remain scarce.

Given the paucity of integrated clinical, microbiological, and cardiopulmonary assessments of CF patients in southeastern Iran, we conducted this retrospective cross-sectional study at Afzalipour Hospital, a major referral center in Kerman Province. The objectives were to delineate the demographic features, age at diagnosis, growth status, respiratory microbiology, chest imaging patterns, cardiac function indices, and rates of major extrapulmonary complications in a well-characterized CF cohort, thereby providing baseline data to inform local care protocols and future longitudinal studies.

Methods and materials

Study design and setting

This retrospective cross-sectional study was performed at the pediatric CF clinic of Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran. Although the clinic is primarily oriented toward pediatric care, the center follows cystic fibrosis patients longitudinally into adulthood, and adult patients who received ongoing CF care at this center during the study period were also included. The study period spanned 36 months, from March 2021 to March 2024.

Participants and sampling

All patients with a confirmed diagnosis of CF who attended the clinic during the study period were identified through the hospital's electronic registry. Inclusion criteria were: (1) definitive CF diagnosis based on a positive sweat chloride test (chloride concentration > 60 mEq/L) and/or identification of two disease-causing *CFTR* mutations; sweat chloride testing, performed by quantitative pilocarpine iontophoresis, was available for all enrolled patients; CFTR mutation analysis had been performed in 22 patients (31.9%. Other medical conditions associated with false-positive sweat chloride results (e.g., severe malnutrition, adrenal insufficiency, hypothyroidism, and ectodermal dysplasia) were clinically evaluated and excluded. Additionally, patients had to meet the criterion of (2) a clinically stable condition, defined as no pulmonary exacerbation in the preceding six months. Exclusion criteria were a documented history of congenital heart disease or any prior cardiac surgery. A total of 69 patients met these eligibility criteria and were included using a census sampling approach.

Data collection

Medical records were systematically reviewed by a single investigator using a standardized data extraction form. The following variables were recorded:

- Demographic and baseline characteristics: age at study entry, sex, age at diagnosis, birth weight, current weight, consanguinity of parents, family history of CF.
- Diagnostic parameters included sweat chloride concentration, measured using quantitative pilocarpine iontophoresis, and CFTR mutation analysis when available. Sweat chloride testing was performed in all 69 enrolled patients, whereas CFTR mutation analysis was available for 22 patients (31.9%).
- Initial clinical presentation: respiratory symptoms, steatorrhea, salty skin, prolonged jaundice, meconium ileus, and failure to thrive (FTT) at first presentation.
- Growth and nutritional status: presence of FTT (defined as weight-for-age below the 3rd percentile or a drop of two or more major percentile lines over time), delayed puberty (assessed by Tanner staging; absence of breast development by age 13 years in girls and testicular volume < 4 mL by age 14 years in boys). Anthropometric data included current weight, height, and body mass index (BMI). Weight-for-age z-score (WAZ) was calculated for patients aged < 10 years, while height-for-age z-score (HAZ) and BMI-for-age z-score (BMIZ) were calculated for patients aged 5–19 years according to WHO reference standards. Because WHO age-based z-score standards do not apply to adults, BMI was calculated and reported as a raw value (kg/m^2) for patients aged ≥ 20 years [18].
- Respiratory history: number of lifetime hospitalizations, hospitalizations for respiratory causes, history of bronchiolitis, recurrent pneumonia, bronchitis, clubbing, nasal polyps, chronic rhinosinusitis; need for supplemental oxygen or non-invasive ventilation (NIV); daily frequency of nebulization and chest physiotherapy; use of inhaled antibiotics (tobramycin, amikacin). The types of nebulized medications recorded were bronchodilators, hypertonic saline, and inhaled antibiotics (specifically tobramycin and amikacin), which were prescribed

based on clinical indications and microbiological findings. The primary airway clearance technique (ACT) utilized in our center is conventional chest physiotherapy, comprising postural drainage and manual percussion. These sessions are tailored to the patient's age and clinical severity, with extensive education provided to caregivers for home-based adherence**.**

- Hospitalization data were collected as the total number of hospital admission episodes for each patient, rather than the duration of hospitalization or the number of inpatient days. We recorded gastrointestinal-related hospitalizations based on available clinical documentation. However, the specific diagnosis or indication for each gastrointestinal admission was not consistently retrievable from the retrospective database.
- Pulmonary function: data were obtained from available spirometry records. Since spirometry is effort-dependent and requires adequate cooperation, it was available only in a subgroup of patients who were able to perform acceptable maneuvers. Additional respiratory assessments, including the six-minute walk test, lung clearance index, polysomnography, and spirometry, were recorded when available.
- Microbiological data: included the results of sputum or deep throat swab cultures for routine aerobic bacteria and, when clinically requested, fungi**.** Antimicrobial susceptibility testing was performed using the Kirby–Bauer disc diffusion method according to CLSI guidelines, and the presence of multidrug-resistant (MDR) isolates was recorded. Anaerobic cultures were not routinely performed during the study period.
- Microbiological Surveillance and Definitions

  Respiratory samples were obtained during routine clinic visits or hospital admissions. In patients capable of expectorating, sputum samples were collected (n = 41). In non-expectorating younger pediatric patients, deep throat swabs (n = 28) were obtained by experienced clinical staff. Cultures were performed at least quarterly for clinically stable patients, and additionally during episodes of pulmonary exacerbation. Because the retrospective database was organized at the patient level, individual culture results could not always be temporally linked to a specific pulmonary exacerbation episode.

  Chronic colonization was defined using the modified Leeds criteria: patients were classified as chronically colonized if > 50% of respiratory samples collected during the preceding 12 months (with a minimum of 4 samples per year) were positive for a specific pathogen (e.g., *Pseudomonas aeruginosa*). The isolation of a microorganism from a respiratory specimen alone was not considered sufficient evidence of active infection. Microbiological findings were interpreted together with the patient's clinical condition and treatment history. Multidrug resistance (MDR) was defined as non-susceptibility to at least one agent in three or more antimicrobial categories clinically relevant to the pathogen
- Chest CT findings: presence and type of structural lung damage (bronchiectasis, cylindrical bronchiectasis, signet-ring sign, ground-glass opacity, mucous plugging, bronchial wall thickening, pulmonary nodules, alveolar hemorrhage).
- Cardiac evaluation: two-dimensional and Doppler echocardiography data including left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), estimated systolic pulmonary artery pressure (SPAP), left and right ventricular dysfunction, and severity of valvular regurgitation (mitral, tricuspid, aortic, pulmonic). Right ventricular (RV) systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE). To account for age and body size, age-appropriate criteria were used to define abnormal TAPSE. For pediatric patients (< 18 years of age), TAPSE values were converted to age-adjusted Z-scores based on the reference data reported by Koestenberger et al. [19], and a Z-score <−2 was considered abnormal. For adult patients (≥ 18 years of age), abnormal TAPSE was defined using the conventional cutoff of < 17 mm. TAPSE classification was performed at the individual patient level according to the applicable age-specific criterion [19]. Furthermore, right ventricular (RV) dysfunction was defined as a qualitative echocardiographic assessment of reduced RV systolic function based on visual evaluation by the treating cardiologist, whereas TAPSE provided a quantitative, age-adjusted measure of RV systolic excursion. These two assessments were therefore complementary but not interchangeable: abnormal TAPSE (Z-score <− 2 in pediatric patients or

< 17 mm in adults) reflects subclinical impairment of RV systolic function, whereas RV dysfunction represents a clinical/qualitative diagnosis of overt ventricular compromise.

- Echocardiographic evaluation was performed systematically for all enrolled patients ($N = 69$) as part of their routine annual cardiac assessment. Chest high-resolution computed tomography (HRCT) was performed in all enrolled patients (N = 69) to assess pulmonary structural abnormalities.

  Gastrointestinal and metabolic complications: number of gastrointestinal-related hospitalizations, history of gastrointestinal surgery, diagnosis of CFRD (based on fasting glucose, oral glucose tolerance test, or HbA1c according to American Diabetes Association criteria), liver cirrhosis (confirmed by clinical, laboratory, or biopsy findings).

Operational definitions

- *Pulmonary exacerbation*: acute worsening of at least two of the following: cough frequency, sputum volume or purulence, dyspnea, anorexia, weight loss, or decline in lung function, requiring a change in antibiotic regimen. Accordingly, a positive culture was considered clinically relevant when interpreted in the context of compatible clinical deterioration and/or a documented pulmonary exacerbation, rather than being classified as active infection solely based on microbial isolation. It is important to note that hospital admission was considered a clinical decision pathway for patients failing outpatient therapy or presenting with severe clinical symptoms, rather than a primary operational definition of exacerbation severity.
- *CFRD*: diagnosis documented in the medical record per ADA guidelines.
- *Delayed puberty*: defined as above, recorded by the treating endocrinologist.
- Histories of *bronchiolitis, bronchitis*, and recurrent *pneumonia* were extracted from the patients' medical records and referral documentation based on diagnoses previously documented by the treating physicians. Because of the retrospective design, these conditions were not reassessed using predefined study-specific clinical, radiographic, laboratory, or age-based criteria. Accordingly, the reported frequencies refer to documented historical diagnoses rather than independently adjudicated episodes.
- For TAPSE interpretation, participants were categorized as pediatric (< 18 years) or adult (≥ 18 years). BMI was analyzed using adult criteria only for participants aged ≥ 20 years.

Ethical considerations

The study protocol was approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1404.203) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature, the requirement for informed consent was waived. All data were anonymized and stored securely, accessible only to the research team.

Statistical analysis

Data were entered into SPSS version 26.0. Descriptive statistics are presented as frequencies (percentages) for categorical variables and mean ± standard deviation for continuous variables. For continuous variables with a non-normal distribution, data are presented as median with interquartile range (IQR) in addition to mean ± SD. Comparisons between sexes were performed using the chi-square (χ^2) test for categorical variables and the independent-samples t-test or Mann–Whitney U test for continuous variables, as appropriate. The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were compared using

the independent t-test, while non-normally distributed data were compared using the Mann–Whitney U test. A two-sided P-value <0.05 was considered statistically significant.

Exploratory multivariable logistic regression analyses

To investigate factors associated with major clinical outcomes, univariable logistic regression analyses were initially performed. Given the sample size and number of outcome events, exploratory multivariable logistic regression models were constructed only for outcomes with adequate event counts, namely bronchiectasis, chronic Pseudomonas aeruginosa colonization, and failure to thrive (FTT). Variables meeting the prespecified univariable screening criterion ($P<0.20$) were considered for inclusion in the multivariable models. Multivariable analysis was not performed for elevated systolic pulmonary artery pressure (SPAP), CFRD, or liver cirrhosis because of the low event frequencies. These multivariable analyses were considered exploratory and hypothesis-generating, and the findings were interpreted cautiously in view of the small sample size and potential residual confounding.

Results

A total of 69 patients with CF were studied. Demographic and baseline characteristics by sex are summarized in Table 1. The distribution of age at diagnosis was positively skewed, with a median (IQR) of 14.0 (4.0–48.0) months overall. Males had a median age at diagnosis of 12.0 (4.0–24.0) months, whereas females had a wider range with a median of 24.0 (5.0–72.0) months, reflecting several late-diagnosed cases in the female subgroup.

Because anthropometric Z-scores were interpreted according to age-specific WHO reference standards, these indices were analyzed only in age-eligible subgroups. Height-for-age Z-score (HAZ) and BMI-for-age Z-score (BMIZ) were assessed in patients aged <20 years (n = 41), whereas weight-for-age Z-score (WAZ) was reported only for patients within the valid age range for this index (n = 14). For patients aged ≥ 20 years, BMI was reported separately as kg/m^2 (n = 11). Therefore, the denominators for anthropometric variables differed from those of the full cohort. Nutritional impairment based on WHO-derived Z-scores was reported separately from the clinical

Table 1 Demographic and baseline characteristics of the study population

Variable	Total (N = 69)	Male (n = 40)	Female (n = 29)	P-value
Age, years, mean ± SD	10.07 ± 7.53	9.97 ± 6.61	10.21 ± 8.75	0.855
Birth weight, kg, mean ± SD	2.80 ± 0.55	2.78 ± 0.59	2.84 ± 0.50	0.595
Current weight, kg, mean ± SD	26.78 ± 15.77	28.57 ± 16.80	24.29 ± 14.14	0.398
Consanguineous parents, n (%)	45 (65.2)	23 (57.5)	22 (75.9)	0.185
Family history of CF, n (%)	20 (29.0)	11 (27.5)	9 (31.0)	0.960
Failure to thrive, n (%)	53 (76.8)	30 (75.0)	23 (79.3)	0.897
Delayed puberty, n (%)	3 (4.3)	2 (5.0)	1 (3.4)	1.000
History of COVID-19, n (%)	6 (8.7)	1 (2.5)	5 (17.2)	0.076
Weight-for-age Z-score (WAZ), mean ± SD, age-eligible patients only (n = 14, 6 male, 8 female)	− 2.31 ± 0.89	− 2.28 ± 0.85	− 2.35 ± 0.94	0.712
Height-for-age Z-score (HAZ), mean ± SD, (age-eligible patients only: n = 41)	− 1.42 ± 1.21	− 1.38 ± 1.18	− 1.47 ± 1.26	0.654
BMI-for-age Z-score (BMIZ), mean ± SD, (age-eligible patients only: n = 41, 24 male, 17 female)	− 2.18 ± 0.94	− 2.12 ± 0.91	− 2.26 ± 0.98	0.601
BMI For patients aged ≥ 20 (kg/m^2), mean ± SD, n = 11(6 male, 5 female)	17.1 ± 5.6	17.28 ± 6.25	16.98 ± 3.7	0.929

Values are presented as mean ± SD or number (%), as appropriate. Anthropometric z-scores were calculated only in age-eligible subgroups according to WHO reference standards: WAZ for patients aged <10 years (n = 14), and HAZ/BMIZ for patients aged 5–19 years (n = 41). For patients aged ≥ 20 years (n = 11), BMI was calculated and reported as a raw value (kg/m^2), because age-based z-score references do not apply to adults

Table 2 Diagnostic features and initial clinical presentations

Variable	Total (N = 69)	Male (n = 40)	Female (n = 29)	P-value
Age at diagnosis, months				0.410
Mean ± SD	44.41 ± 27.13	28.86 ± 18.65	65.86 ± 38.83	
Median [IQR]	14.0 [4.0–48.0]	12.0 [4.0–24.0]	24.0 [5.0–72.0]	
Sweat chloride, mEq/L, mean ± SD	94.04 ± 29.80	96.00 ± 33.58	91.34 ± 23.95	0.803
Genetic test performed, n (%)	22 (31.9)	12 (30.0)	10 (34.5)	0.894
Initial respiratory symptoms, n (%)	53 (76.8)	29 (72.5)	24 (82.8)	0.479
Initial gastrointestinal symptoms, n (%)	28 (40.6)	17 (42.5)	11 (37.9)	0.894
FTT at initial presentation, n (%)	42 (60.9)	25 (62.5)	17 (58.6)	0.939
Prolonged jaundice, n (%)	13 (18.8)	8 (20.0)	5 (17.2)	1.000
Meconium ileus, n (%)	7 (10.1)	5 (12.5)	2 (6.9)	0.690
Steatorrhea, n (%)	67 (97.1)	39 (97.5)	28 (96.6)	1.000
Salty skin, n (%)	58 (84.1)	35 (87.5)	23 (79.3)	0.507

SD: standard deviation; FTT: failure to thrive

Data for age at diagnosis are presented as median [IQR] (first quartile, third quartile) due to the highly skewed distribution and the presence of outliers (e.g., patients diagnosed in late adulthood). The statistical comparison between male and female subgroups was performed using the Mann–Whitney U test. The wide standard deviations reflect considerable inter-individual variability, particularly in the female subgroup, due to a few late-diagnosed cases

Sweat chloride testing was performed for all 69 patients (100.0%) using quantitative pilocarpine iontophoresis, whereas genetic testing was available for 22 patients (31.9%)

Table 3 Respiratory history and clinical severity indicators

Variable	Total (N = 69)	Male (n = 40)	Female (n = 29)	P-value
Number of lifetime hospitalizations, mean ± SD	4.77 ± 3.49	4.28 ± 3.29	5.45 ± 3.71	0.195
Number of respiratory hospitalizations, mean ± SD	3.62 ± 3.02	3.15 ± 2.63	4.28 ± 3.43	0.175
Documented history of bronchiolitis, n (%)	45 (65.2)	26 (65.0)	19 (65.5)	1.000
Documented history of recurrent pneumonia, n (%)	45 (65.2)	23 (57.5)	22 (75.9)	0.185
Documented history of bronchitis, n (%)	33 (47.8)	15 (37.5)	18 (62.1)	0.076
Clubbing, n (%)	28 (40.6)	16 (40.0)	12 (41.4)	1.000
Nasal polyps, n (%)	20 (29.0)	12 (30.0)	8 (27.6)	1.000
Chronic rhinosinusitis, n (%)	8 (11.6)	4 (10.0)	4 (13.8)	0.712

SD: standard deviation. These variables were extracted from previously documented diagnoses in the medical records and were not independently reassessed using predefined study-specific diagnostic criteria

diagnosis of FTT. In the age-eligible subgroups, mean WAZ was − 2.31 ± 0.89, mean HAZ was − 1.42 ± 1.21, and mean BMIZ was − 2.18 ± 0.94, indicating a substantial burden of undernutrition. Among patients aged ≥ 20 years, mean BMI was 17.1 ± 5.6 kg/m^2.

Table 2 presents diagnostic indicators and initial clinical manifestations. The mean age at diagnosis was 44.41 ± 27.13 months (approximately 4 years), and the mean sweat chloride concentration was 94.04 ± 29.80 mEq/L. Genetic testing was performed in 22 patients (31.9%). Detailed CFTR variant data were not consistently available in the medical records. The most common presenting symptoms were steatorrhea (97.1%), salty skin (84.1%), respiratory symptoms (76.8%), and FTT at initial presentation (60.9%). Meconium ileus was documented in 7 neonates (10.1%).

Respiratory history and markers of clinical severity are summarized in Table 3. The mean frequency (number of episodes) of lifetime hospitalizations was 4.77 ± 3.49, and the mean number of respiratory-related hospitalizations

Table 4 Respiratory support and airway clearance therapies

Variable	Total (N = 69)	Male (n = 40)	Female (n = 29)	P-value
Need for oxygen, n (%)	9 (13.0)	4 (10.0)	5 (17.2)	0.477
Need for NIV, n (%)	5 (7.2)	4 (10.0)	1 (3.4)	0.389
Nebulization frequency per day, mean ± SD	2.14 ± 0.90	1.93 ± 0.76	2.45 ± 0.99	0.037
Chest physiotherapy per day, mean ± SD	2.14 ± 0.90	1.93 ± 0.76	2.45 ± 0.99	0.037
Use of inhaled tobramycin, n (%)	29 (42.0)	14 (35.0)	15 (51.7)	0.253
Use of inhaled amikacin, n (%)	20 (29.0)	10 (25.0)	10 (34.5)	0.556

NIV: non-invasive ventilation; SD: standard deviation. Significant P-values are highlighted in bold. Supplemental oxygen included any documented oxygen requirement, whereas long-term home oxygen referred specifically to chronic home use

Table 5 Respiratory culture results and isolated pathogens

Variable	Total (N = 69)	Male (n = 40)	Female (n = 29)	P-value
Positive respiratory culture, n (%)	38 (55.1)	20 (50.0)	18 (62.1)	0.453
Pseudomonas aeruginosa, n (%)	30 (43.5)	15 (37.5)	15 (51.7)	0.352
Staphylococcus aureus, n (%)	19 (27.5)	11 (27.5)	8 (27.6)	1.000
Streptococcus viridans, n (%)	5 (7.2)	1 (2.5)	4 (13.8)	0.154
Non-hemolytic *Streptococcus*, n (%)	9 (13.0)	6 (15.0)	3 (10.3)	0.724
Escherichia coli, n (%)	4 (5.8)	0 (0.0)	4 (13.8)	**0.027**
Enterococcus spp., n (%)	1 (1.4)	0 (0.0)	1 (3.4)	0.420
Candida spp., n (%)	3 (4.3)	0 (0.0)	3 (10.3)	0.070

SD: standard deviation. Multiple pathogens could be isolated from a single patient; therefore, the sum of isolates exceeds the number of culture-positive patients

was 3.62 ± 3.02. A documented history of at least one episode of bronchiolitis was present in 45 patients (65.2%), while documented histories of recurrent pneumonia and bronchitis were present in 45 (65.2%) and 33 patients (47.8%), respectively. Clubbing was present in 28 patients (40.6%), nasal polyps in 20 (29.0%), and chronic rhinosinusitis in 8 (11.6%). No significant sex differences were observed for these variables.

Respiratory management strategies are shown in Table 4. Nine patients (13.0%) required supplemental oxygen and 5 (7.2%) needed NIV. The mean daily frequency of nebulization and chest physiotherapy was 2.14 ± 0.90, and this was significantly higher in females (2.45 ± 0.99) than in males (1.93 ± 0.76; P = 0.037). Nebulized therapies included bronchodilators and hypertonic saline for airway clearance, as well as inhaled antibiotics prescribed when clinically indicated according to microbiological findings. Inhaled tobramycin had been prescribed to 29 patients (42.0%), whereas inhaled amikacin had been prescribed to 20 patients (29.0%).

Regarding respiratory support, 8 patients (11.6%) required long-term home oxygen therapy, and 5 patients (7.2%) required non-invasive ventilation (NIV). Two patients in this cohort required invasive mechanical ventilation or endotracheal intubation during the study period.

Three patients (4.3%) died during the study period, all secondary to end-stage cardiopulmonary failure and severe pulmonary complications in the setting of advanced cardiopulmonary disease with documented chronic Pseudomonas aeruginosa colonization. Contributing complications included severe pulmonary hypertension (SPAP > 35 mmHg) with right ventricular dysfunction (n = 2) and massive pulmonary hemorrhage/hemoptysis (n = 2). These conditions were not mutually exclusive; one patient presented with the co-occurrence of both severe pulmonary hypertension and massive pulmonary hemorrhage.

Microbiological culture results are presented in Table 5. Respiratory cultures were positive in 38 patients (55.1%). Pseudomonas aeruginosa was isolated from 30 patients (43.5%) and Staphylococcus aureus from 19 (27.5%). These figures represent respiratory microorganism isolation and should not be interpreted as evidence that every isolated organism caused an active infection. Escherichia coli was exclusively identified in 4 female

patients (13.8%) and in none of the males (P = 0.027). No significant sex difference was observed for other pathogens.

Among the 69 patients, the most frequently isolated pathogens were Pseudomonas aeruginosa (n = 30, 43.5%) and Staphylococcus aureus (n = 19, 27.5%). Chronic colonization with *P. aeruginosa* was identified in 15 patients (21.7% of the total cohort; 50.0% of those with *P. aeruginosa* isolation). Antimicrobial susceptibility testing showed that resistance among *P. aeruginosa* isolates was highest to ceftazidime (35.7%) and ciprofloxacin (28.6%), whereas amikacin (14.3% resistance) and colistin (3.6% resistance) retained the greatest activity. Multidrug-resistant *P. aeruginosa* was identified in 5 isolates (16.7% of *P. aeruginosa* isolates). Among *S. aureus* isolates, methicillin resistance (MRSA) was confirmed in 6 patients (31.6% of *S. aureus* isolates).

More than one microorganism could be isolated from the respiratory specimens of the same patient; therefore, the organism-specific counts were not mutually exclusive, and their sum exceeded the number of culture-positive patients. Because of the retrospective patient-level structure of the database, these isolates could not consistently be assigned to the same pulmonary exacerbation episode.

Pulmonary Function Testing (Spirometry) is presented in Table 6. Spirometry was performed in a subset of 36 patients (52.2% of the cohort) who were old enough to cooperate and had accessible records. The mean forced expiratory volume in 1 s (FEV_1) was 73.4% ± 16.8% of predicted, and the mean forced vital capacity (FVC) was 82.1% ± 14.5% of predicted. The mean FEV_1/FVC ratio was 78.6% ± 11.2%.

Based on FEV_1% predicted values, pulmonary impairment was classified as normal (≥ 90%) in 8 patients (22.2%), mild (70–89%) in 13 patients (36.1%), moderate (40–69%) in 12 patients (33.3%), and severe (< 40%) in 3 patients (8.3%) (Table 6).

Pulmonary structural abnormalities on chest CT and systemic complications are summarized in Table 7. Pulmonary structural abnormalities were detected in 36 patients (52.2%). Bronchiectasis was present in 35 patients (50.7%), the signet-ring sign in 22 (31.9%), cylindrical bronchiectasis in 8 (11.6%), ground-glass opacity in 6 (8.7%), bronchial wall thickening in 6 (8.7%), mucous plugging in 4 (5.8%), and pulmonary nodules in 1 (1.4%). Pulmonary hemorrhage was noted in 3 patients (4.3%).

Regarding extrapulmonary and gastrointestinal complications (Table 7), the mean number of GI-related hospital admission episodes per patient was 1.30 ± 1.06. Nine patients (13.0%) had a history of gastrointestinal surgery. CF-related diabetes and liver cirrhosis were each documented in 2 patients (2.9%). Because the specific indications for individual gastrointestinal admissions were not systematically recorded in the retrospective database, the causes of these admissions could not be categorized further.

Overall, echocardiographic abnormalities were identified in 26 patients (37.7%) based on abnormal TAPSE, with left ventricular dysfunction in 10 (14.5%), right ventricular dysfunction in 8 (11.6%), and elevated SPAP in 5 (7.2%), as shown in Table 8.

Table 6 Lung function parameters in the spirometry subgroup (n = 36)

Parameter	Value (Mean ± SD) or n (%)
Spirometry Subgroup	n = 36
FEV_1(% predicted)	73.4 ± 16.8
FVC(% predicted)	82.1 ± 14.5
FEV_1/**FVC** ratio (%)	78.6 11.2
Severity of Lung Disease (based on FEV_1)	
Normal (≥ 90%)	8 (22.2%)
Mild impairment (70–89%)	13 (36.1%)
Moderate impairment (40–69%)	12 (33.3%)
Severe impairment (< 40%)	3 (8.3%)

FEV1: Forced Expiratory Volume in 1 s; FVC: Forced Vital Capacity

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Table 7 Chest CT findings, systemic complications, and GI-related hospital admission episodes per patient

Variable	Total (N = 69)	Male (n = 40)	Female (n = 29)	P-value
Any pulmonary complication, n (%)	36 (52.2)	20 (50.0)	16 (55.2)	0.857
Bronchiectasis, n (%)	35 (50.7)	18 (45.0)	17 (58.6)	0.383
Signet-ring sign, n (%)	22 (31.9)	12 (30.0)	10 (34.5)	0.894
Cylindrical bronchiectasis, n (%)	8 (11.6)	6 (15.0)	2 (6.9)	0.453
Ground-glass opacity, n (%)	6 (8.7)	3 (7.5)	3 (10.3)	0.690
Mucous plug, n (%)	4 (5.8)	2 (5.0)	2 (6.9)	1.000
Bronchial wall thickening, n (%)	6 (8.7)	3 (7.5)	3 (10.3)	0.690
Pulmonary nodule, n (%)	1 (1.4)	1 (2.5)	0 (0.0)	1.000
Pulmonary hemorrhage, n (%)	3 (4.3)	1 (2.5)	2 (6.9)	0.568
GI hospitalizations, mean ± SD	1.30 ± 1.06	1.25 ± 1.02	1.40 ± 1.10	0.897
GI surgery history, n (%)	9 (13.0)	5 (12.5)	4 (13.8)	1.000
CF-related diabetes, n (%)	2 (2.9)	1 (2.5)	1 (3.4)	1.000
Liver cirrhosis, n (%)	2 (2.9)	0 (0.0)	2 (6.9)	0.173

GI: gastrointestinal. GI-related hospitalizations represent the number of documented admission episodes per patient and not the number of inpatient days or length of stay

Table 8 Echocardiographic findings and cardiac function in cystic fibrosis patients

Variable	Total (***n* = 69**)	Male (***n* = 40**)	Female (***n* = 29**)	*P*-value
Overt cardiac failure, n (%)	8 (11.6)	5 (12.5)	3 (10.3)	1.000
LVEF (%), mean ± SD	58.88 ± 2.95	59.08 ± 2.23	58.62 ± 3.76	0.826
Left ventricular dysfunction, n (%)	10 (14.5)	6 (15.0)	4 (13.8)	0.436
Right ventricular dysfunction, n (%)	8 (11.6)	4 (10.0)	4 (13.8)	0.712
Pulmonary hypertension (SPAP > 35 mmHg), n (%)	5 (7.2)	3 (7.5)	2 (6.9)	1.000
TAPSE (mm), mean ± SD	14.56 ± 2.94	14.65 ± 2.76	14.43 ± 3.23	0.777
Overall TAPSE status, n (%)				1.000
Normal	43 (62.3)	25 (62.5)	18 (62.1)	
Abnormal*	26 (37.7)	15 (37.5)	11 (37.9)	
Age-stratified TAPSE status, n/N (%)				
Pediatric patients (< 18 years, N = 58)		*n* = 33	*n* = 25	1.000
Normal (TAPSE Z-score ≥ −2)	37/58 (63.8)	22/33 (66.7)	15/25 (60.0)	
Abnormal (TAPSE Z-score < −2)	21/58 (36.2)	11/33 (33.3)	10/25 (40.0)	
Adult patients (≥ 18 years, N = 11)		*n* = 7	*n* = 4	1.000
Normal (TAPSE ≥ 17 mm)	6/11 (54.5)	3/7 (42.9)	3/4 (75.0)	
Abnormal (TAPSE < 17 mm)	5/11 (45.5)	4/7 (57.1)	1/4 (25.0)	
Valvular regurgitation (≥ mild), n (%)				
Tricuspid regurgitation	7 (10.1)	4 (10.0)	3 (10.3)	1.000
Aortic regurgitation	4 (5.8)	2 (5.0)	2 (6.9)	1.000
Pulmonic regurgitation	4 (5.8)	3 (7.5)	1 (3.4)	0.634

LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; SD: standard deviation

*Abnormal TAPSE was defined using an age-adjusted Z-score < −2 in pediatric patients (< 18 years) according to Koestenberger et al. reference values [19], and TAPSE < 17 mm in adult patients (≥ 18 years)

P-values were calculated using the independent Student's t-test/Mann–Whitney U test for continuous variables and Pearson's chi-square or Fisher's exact test for categorical variables.

Among the 58 pediatric patients (< 18 years), 21 (36.2%) had an abnormal TAPSE Z-score (< −2), whereas 5 of the 11 adult patients (≥ 18 years) had an abnormal TAPSE (< 17 mm). Thus, 26 of 69 patients (37.7%) were

classified as having abnormal TAPSE overall.

Factors associated with clinical outcomes

Exploratory multivariable logistic regression analyses were performed for three outcomes with adequate event counts across the total cohort (N = 69): bronchiectasis (n = 35, 50.7%), chronic Pseudomonas aeruginosa colonization (n = 15, 21.7%), and failure to thrive (FTT; n = 53, 76.8%). The results are summarized in Table 9.

In the multivariable model for bronchiectasis (35 events/69 patients), bronchiectasis remained associated after adjustment with chronic Pseudomonas aeruginosa colonization (aOR = 3.12, 95% CI 1.18–8.26, P = 0.022), a history of recurrent pneumonia (aOR = 2.85, 95% CI 1.02–7.96, P = 0.045), and younger age at diagnosis (aOR = 0.89 per year increase, 95% CI 0.80–0.99, P = 0.038).

In the model for chronic *P. aeruginosa* colonization (15 events/69 patients), colonization remained associated after adjustment for older age at diagnosis (aOR = 1.12 per year increase, 95% CI 1.01–1.24, P = 0.031) and inhaled tobramycin use (aOR = 3.68, 95% CI 1.32–10.26, P = 0.013). A history of recurrent pneumonia showed a borderline association (aOR = 2.56, 95% CI 0.98–6.69, P = 0.055).

Elevated systolic pulmonary artery pressure (SPAP >= 35 mmHg) was documented in only 5 patients (7.2%), precluding multivariable analysis due to the limited number of events. In univariate analysis, patients with elevated SPAP had higher rates of bronchiectasis (80.0% vs. 48.4%, P = 0.176) and abnormal TAPSE (60.0% vs. 35.9%, P = 0.290), although these differences did not reach statistical significance.

For failure to thrive (53 events/69 patients), FTT remained associated after adjustment with younger age at diagnosis (aOR = 0.92 per year increase, 95% CI 0.85–0.99, P = 0.032), whereas meconium ileus (aOR = 3.21, 95% CI 0.91–11.34, P = 0.069) and chronic Pseudomonas aeruginosa colonization (aOR = 2.18, 95% CI 0.94–5.06, P = 0.069) showed borderline associations.

Table 9 Exploratory multivariable logistic regression analysis of factors associated with clinical outcomes

Outcome (Events/Total patients)	Independent variable	aOR	95% CI	P-value
Bronchiectasis (n = 35/69, 50.7%)	Chronic Pseudomonas aeruginosa colonization	3.12	1.18–8.26	0.022
	History of recurrent pneumonia	2.85	1.02–7.96	0.045
	Age at diagnosis (per year increase)	0.89	0.80–0.99	0.038
Chronic *P. aeruginosa* colonization (n = 15/69, 21.7%)	Age at diagnosis (per year increase)	1.12	1.01–1.24	0.031
	Inhaled tobramycin use	3.68	1.32–10.26	0.013
	History of recurrent pneumonia	2.56	0.98–6.69	0.055
Failure to Thrive (FTT) (n = 53/69, 76.8%)	Age at diagnosis (per year increase)	0.92	0.85–0.99	0.032
	Meconium ileus	3.21	0.91–11.34	0.069
	Chronic Pseudomonas aeruginosa colonization	2.18	0.94–5.06	0.069

aOR: adjusted odds ratio; CI: confidence interval. Candidate variables with P < 0.20 in univariate analysis were entered into the multivariable logistic regression models. Multivariable models were constructed only for outcomes with adequate event counts:

The bronchiectasis model was adjusted for Chronic Pseudomonas aeruginosa colonization, history of recurrent pneumonia, age at diagnosis, and sex

The chronic *P. aeruginosa* colonization model was adjusted for age at diagnosis, inhaled tobramycin use, and history of recurrent pneumonia

The failure to thrive model was adjusted for age at diagnosis, meconium ileus, and *P. aeruginosa* colonization

Due to low event counts (elevated SPAP: n = 5; CF-related diabetes: n = 2; liver cirrhosis: n = 2), multivariable regression modeling was not feasible for these outcomes. Given the modest cohort size and limited event numbers per variable, all multivariable findings should be interpreted strictly as exploratory and hypothesis-generating

Discussion

This study provides a multidimensional cross-sectional portrait of CF patients managed at a single referral center in southeastern Iran. Several findings warrant detailed reflection. The mean age at diagnosis of approximately 4 years is markedly delayed compared with regions that have implemented universal newborn screening, where diagnosis is typically established in the first months of life [4, 7]. This diagnostic lag is consistent with previous reports from Iran and neighboring countries, where limited awareness, scarce sweat testing facilities, and the absence of a national screening program continue to hinder timely identification [8, 10]. The high rate of consanguinity (65.2%) and positive family history (29.0%) in our cohort echoes earlier regional reports and underscores the importance of family-based risk assessment, access to diagnostic testing, and genetic counseling in communities with elevated background consanguinity [9].

Nearly 77% of our patients exhibited FTT at evaluation, a proportion that exceeds figures from well-resourced CF centers where aggressive nutritional support maintains normal growth in a substantial fraction of children [16, 20]. This discrepancy may stem from the delayed initiation of pancreatic enzyme replacement therapy and high-calorie supplementation, compounded by recurrent pulmonary exacerbations that increase metabolic demand. The prominence of steatorrhea (97%) and FTT at initial presentation underscores the profound gastrointestinal involvement that often precedes respiratory deterioration, a pattern that aligns with the natural history of CF [15].

The substantial burden of malnutrition in our cohort is unequivocally demonstrated by the anthropometric Z-scores, which fell well below WHO thresholds for significant undernutrition across all age-eligible subgroups. These values are markedly inferior to those reported from well-resourced CF registries, such as the U.S. Cystic Fibrosis Foundation and European Cystic Fibrosis Society registries, where mean BMI Z-scores typically range between −0.8 and −1.5 [20, 21]. The nearly 1.0–1.5 standard deviation gap observed in our population is clinically consequential, as each unit increase in BMI Z-score has been linked to a 15–20% reduction in pulmonary exacerbation risk and better lung function preservation [22]. This discrepancy likely stems from delayed diagnosis (mean age ~4 years), suboptimal access to pancreatic enzyme replacement therapy and nutritional supplements, and socioeconomic barriers to treatment adherence [16, 23].

Furthermore, high consanguinity may contribute to a greater burden of recessive disease and potentially more severe clinical phenotypes, although genotype-level confirmation was unavailable in most patients [9]. These findings collectively underscore the critical need for structured, multidisciplinary nutritional interventions, including proactive dietitian support, aggressive enzyme replacement, and timely consideration of enteral feeding, as advocated by international CF nutrition guidelines [24, 25].

The respiratory microbiology of our patients is dominated by *P. aeruginosa* and *S. aureus*, mirroring the classic CF infection paradigm [12, 13]. However, the exclusive isolation of *E. coli* from female patients, albeit in a small number, raises intriguing questions. Potential explanations include contamination from perineal flora during specimen collection in young children, true sex-based differences in oropharyngeal flora, or microaspiration of gastrointestinal contents in females with more severe reflux, though none can be confirmed with the available data. This finding should be interpreted cautiously and explored in future studies with rigorous sampling protocols. Notably, NTM and *Aspergillus* species were not reported in any culture, an observation that almost certainly reflects the absence of systematic screening rather than true absence. International registries suggest a pooled NTM prevalence of 7–9% in CF populations, and the rising importance of fungal pathogens is well documented [14, 26]. The lack of dedicated AFB and fungal cultures in our center represents a significant diagnostic gap that may delay targeted therapy. To address this limitation, it is worth noting that while systematic, protocol-driven screening for NTM and fungal pathogens was not routinely performed for all patients during the study period, these diagnostic investigations (including mycobacterial cultures and fungal smears/cultures) are currently available at our center's laboratory and affiliated referral facilities. Currently, these tests are requested selectively based on clinical indications, such as unexplained clinical deterioration, failure to respond to standard antibiotic therapy, or atypical radiological findings.

Structural lung disease, particularly bronchiectasis, was present in half of the patients despite a mean age of only 10 years. This relatively early onset of permanent airway damage is consistent with the concept that CF lung disease begins insidiously in infancy and progresses if uncontrolled [22]. The frequency of bronchiectasis in our cohort is comparable to that reported in other Iranian series but higher than that observed in age-matched patients from centers with early and sustained anti-inflammatory and anti-infective strategies [10, 27, 28]. The signet-ring sign, a hallmark of destructive bronchiolitis, was present in one-third of patients, further attesting to the advanced nature of small-airways disease in this group. Consistent with the radiological findings, spirometry performed in the available subgroup demonstrated a mean predicted FEV1 of 73.4%, with approximately 41.6% of patients exhibiting moderate-to-severe airflow limitation (FEV1 < 70% predicted). Although spirometry was available for only a subset of patients, these findings support the substantial burden of pulmonary impairment observed in our cohort.

Overt cardiac failure was documented in 11.6% of patients, while left ventricular dysfunction was present in 14.5% and pulmonary hypertension in 7.2%. In addition, 37.7% of patients had abnormal TAPSE according to age-appropriate criteria, suggesting that quantitative abnormalities of right ventricular systolic excursion were relatively common in this cohort. The mean LVEF was within normal limits, yet the proportion of patients with abnormal TAPSE (37.7%) suggests that subclinical right ventricular dysfunction is already prevalent. These rates are lower than those reported in older CF cohorts, where pulmonary hypertension may affect up to 40% of adults, but are noteworthy in a predominantly pediatric population [17]. As life expectancy increases with improved care and the potential introduction of CFTR modulators, regular echocardiographic surveillance will become increasingly important to detect early right heart strain and institute timely cardiopulmonary interventions.

The apparent low prevalence of CFRD (2.9%) and cirrhosis (2.9%) deserves careful interpretation. Both values are well below the expected rates for CF populations, in which CFRD affects approximately 20% of adolescents and up to 40% of adults, and advanced liver disease occurs in 5–10% [15, 27]. Several factors may account for this discrepancy: (1) the relatively young age of the cohort (mean 10 years) may precede the typical onset of CFRD; (2) screening for CFRD via oral glucose tolerance testing was not systematically performed, leading to underdiagnosis; and (3) liver disease was identified only when clinically overt, missing early stages detectable only by ultrasound elastography or biopsy [29]. Thus, the true burden of these metabolic and hepatobiliary complications is likely underestimated, highlighting the need for protocol-driven annual screening.

To further characterize the determinants of major clinical outcomes, we performed exploratory multivariable analyses. Chronic *Pseudomonas aeruginosa* colonization remained associated with bronchiectasis after adjusting for potential confounders. However, these associations should be interpreted cautiously because the histories of bronchiolitis, bronchitis, and recurrent pneumonia were extracted retrospectively from medical records and referral documentation and were not reassessed using predefined study-specific clinical, radiographic, laboratory, or age-based diagnostic criteria. Thus, these variables represent documented historical diagnoses and may be subject to variability in documentation and diagnostic classification.

Previous literature suggests that chronic *P. aeruginosa* infection/colonization is associated with progressive airway damage [13, 22]; in our cross-sectional study, chronic colonization remained associated with bronchiectasis after adjustment, but causality cannot be inferred. The association between younger age at diagnosis and bronchiectasis is noteworthy and likely reflects a selection bias, wherein patients with more severe, early-onset disease are diagnosed earlier and consequently develop structural lung damage at a younger age [23]. This paradoxical finding underscores the importance of newborn screening programs, which enable diagnosis before the onset of irreversible lung injury [4].

The association between inhaled tobramycin use and Chronic *Pseudomonas aeruginosa* colonization (aOR = 3.68) is likely a reflection of treatment indication bias, as patients with confirmed *P. aeruginosa* infection are more likely to receive inhaled antibiotics, rather than tobramycin causing colonization. This finding should be interpreted with caution and does not imply a causal relationship.

Younger age at diagnosis remained associated with FTT in the exploratory multivariable analysis, consistent with the concept that patients with earlier-onset, more severe pancreatic insufficiency are at higher risk of malnutrition [16]. The borderline association with meconium ileus (aOR = 3.21) further supports this interpretation, as meconium ileus is a marker of severe CFTR dysfunction with profound gastrointestinal involvement [15].

The small number of patients with pulmonary hypertension (n = 5) precluded meaningful multivariable analysis, and we acknowledge this as a limitation. However, the observed trends toward associations with bronchiectasis and abnormal TAPSE are consistent with the known pathophysiology of CF-related pulmonary vascular disease [17]. Larger prospective studies are needed to confirm these relationships.

Additionally, for patients who died (3 patients), clinical variables were extracted from their last available medical records before death; however, detailed survival analysis was beyond the scope of this cross-sectional study.

Our study has several strengths. It integrates demographic, nutritional, microbiological, radiological, and echocardiographic data from a well-defined regional CF cohort, providing a comprehensive baseline that is currently lacking in southeastern Iran. The inclusion of all eligible patients through census sampling minimizes selection bias. However, several limitations must be acknowledged. The retrospective design precludes verification of data completeness and introduces the possibility of recording bias; variables such as socioeconomic status, adherence to therapy, and longitudinal lung function were not consistently available. The single-center setting limits generalizability to other Iranian regions with different genetic and environmental backgrounds. Only 32% of patients had undergone CFTR genotyping, preventing genotype–phenotype correlation and the identification of potentially modulator-responsive mutations, and detailed variant-level data were not systematically retrievable from the medical records. Therefore, this cohort does not support reliable conclusions regarding the regional distribution of CFTR mutations. Additionally, comprehensive genetic testing and genotype–phenotype correlations were not feasible due to resource limitations and the retrospective nature of the study, which represents a limitation of our work.

Furthermore, the absence of systematic screening for NTM, AFB, and TB, together with the lack of molecular microbiome profiling and dedicated surveillance for filamentous fungi, restricted the depth of microbiological characterization. Anaerobic cultures were also not routinely performed. Consequently, the prevalence of TB, NTM, anaerobic bacterial infection, and fungal disease could not be reliably determined. In addition, because the database was retrospective and patient-based, individual isolates could not always be linked to a specific pulmonary exacerbation episode. Although spirometry data were available for approximately half of the cohort, longitudinal pulmonary function measurements were not consistently available, precluding assessment of disease progression over time.

Due to the relatively small cohort size and low event frequencies for certain complications—specifically elevated SPAP (n = 5), CFRD (n = 2), and liver cirrhosis (n = 2)—multivariable logistic regression was either precluded or underpowered. Furthermore, while multivariable models were constructed for bronchiectasis, chronic *P. aeruginosa* colonization, and failure to thrive, the relatively limited event-per-variable ratio means that residual confounding or overfitting cannot be excluded. Consequently, all regression findings and observed associations should be interpreted as exploratory and hypothesis-generating, warranting validation in larger multi-center cohorts.

The findings carry clear clinical implications. The late age at diagnosis and high rate of malnutrition argue strongly for piloting newborn screening programs in high-consanguinity regions and for enhancing primary care education on early CF signs. Although chest CT is highly sensitive for detecting early bronchiectasis, the recommendation for periodic screening must be carefully balanced against the risks of cumulative radiation exposure in pediatric patients. In line with current consensus guidelines, routine surveillance should primarily rely on clinical monitoring and pulmonary function testing, reserving low-dose chest CT for specific clinical indications—such as unexplained clinical deterioration, failure to respond to therapy, or before major therapeutic changes—rather than as a routine annual screening tool [25, 31]. The identified microbiological gaps—including the absence of systematic AFB/NTM/TB testing, the lack of routine anaerobic cultures, and limited surveillance for filamentous

fungi—support the implementation of standardized longitudinal microbiological surveillance for NTM, TB, and fungal pathogens in future clinical practice and prospective studies. The observed subclinical right heart abnormalities support a low threshold for echocardiography in patients with declining lung function or nutritional failure. Finally, the establishment of a national CF registry that longitudinally captures clinical, microbiological, and genetic data would facilitate benchmarking, resource allocation, and the design of multicenter interventional trials tailored to the Iranian population [4, 28].

In conclusion, patients with CF at this southeastern Iranian center experience a heavy burden of respiratory infections, early structural lung disease, and nutritional deficits, while extrapulmonary complications, though currently recorded at low frequencies, are likely underrecognized. Strengthening early diagnosis, aggressive nutritional rehabilitation (targeting BMI Z-score ≥ -1.0), systematic microbiological and cardiac surveillance, and broader access to standardized CFTR genetic testing are essential next steps to improve long-term outcomes in this vulnerable population.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate The study was approved by the Ethics Committee of Kerman University of Medical Sciences (reference IR.KMU.AH.REC.1404.203) and conducted in accordance with the Declaration of Helsinki.

Informed consent As this was a retrospective chart review with no patient contact or intervention, the ethics committee waived the requirement for informed consent.

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Azimeh Beigzadeh[1] · Fatemeh Doost-Mohammadi[2] · Maryam Gholami-Shahrebabak[3] · Reza Derakhshan[4] · Azam Gholami-Shahrebabak[3]

✉ Reza Derakhshan
Rderakhshan98@yahoo.com

✉ Azam Gholami-Shahrebabak
aazamgholami67@gmail.com; gholami_a@kmu.ac.ir

Azimeh Beigzadeh
az.beigzadeh@gmail.com

Fatemeh Doost-Mohammadi
f.doostmohammadi2@gmail.com

Maryam Gholami-Shahrebabak
m.gholami@kmu.ac.ir

[1] Department of Pediatrics, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran

[2] Clinical Research Development Unit, Shahid Bahonar Hospital, Kerman University of Medical Sciences, Kerman, Iran

[3] Department of Pediatrics, School of Medicine, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran

[4] Department of Pediatrics, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran