Clinico-Epidemiological Characteristics of Children with Cystic Fibrosis: A Tertiary Care Experience

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Research

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Abstract

Background: Cystic fibrosis (CF) is considered to be rare among individuals from Bangladesh. The objective of the study was to delineate the clinico-epidemiological characteristics of pediatric cystic fibrosis cases.

Method: This observational study included pediatric patients (up to 14 years of age) with a clinical diagnosis of CF. Data were collected within the period from February 2021 and October 2021. Written informed consent was obtained from the accompanying parent. Clinical and epidemiological characteristics were analyzed on the basis of demographic data, medical history, laboratory tests, and outcome information. Data analysis was done with SPSS 26.

Result: A total of 50 patients (66% male) with a mean age of 39.7 ± 30.75 (SD) months were included. Twenty-eight patients (57.14%) had siblings with CF, and 41.67% of parents had a history of consanguineous marriage. The majority of them were stunted (86%) and underweight (86%), and half of them had wasting (54%). Median disease duration was 12 months (range: 2 – 72). Cough (100%) and purulent sputum (100%) were the predominant respiratory symptoms, while failure to thrive (98%) and bulky offensive stools (86%) were prime gastrointestinal symptoms. Among the signs, malnutrition (94%), short stature (72%), digital clubbing (64%), and bronchiectasis (40%) were most frequent. Pulmonary hypertension (48%, n=24) was the most common comorbidity identified in the study participants. In hospital, mortality was 16% (n=8). Digital clubbing, bronchiectasis, pancreatic insufficiency, and abnormal liver function tests were significantly higher in the patient who died.

Conclusion: Children with cystic fibrosis most commonly present with undernutrition and respiratory symptoms. Failure to thrive was almost a global phenomenon. Pulmonary hypertension was the most common complication found in echocardiography.

1. Background

Cystic fibrosis (CF) is a life-limiting classic Mendelian autosomal recessive genetic disorder involving multiple organs, particularly the lungs and digestive system [1]. According to the Cystic Fibrosis Foundation Patient Registry, in the United States, >30,000 people live with cystic fibrosis, and an overall estimate of >70,000 patients live worldwide [2]. The disease is commonly found in Europe, North America, and Australia [3], but significant cases have been reported in Asia, including China, India, and Bangladesh. Although data regarding the prevalence of CF are not ready in hand, several suggestions are that it affects 1/4000 newborns in the US(4), 1/64,000 in China [1], and 1 in 43321 to 1 in 100323 in India [4]. Prevalence data of Bangladesh are currently lacking.

The disease is caused by mutation of a gene that encodes a chloride-conducting transmembrane channel called cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel found in cells lining the lungs, intestines, pancreatic ducts, sweat glands, and reproductive organs. Functional failure of CFTR in the lung results in mucus retention, chronic infection and subsequently small airway obstruction,

and progressive respiratory impairment. Pancreatic dysfunction resulting in malabsorption and other abnormalities, e.g., intestinal obstruction and infertility, are also frequent consequences of CFTR dysfunction [5].

According to history, the median life expectancy for patients with CF was only a few months in the 1950s [6], while during the past six decades, the median age of survival has increased progressively and is now more than 40 years in developed countries [7]. In Asian countries, the majority of them expired within the first 5 years of their life [7–9]. However, understanding the disease process, early identification, treatment of infection, pancreatic enzyme replacement, correction of nutritional deficiency, innovative and transformational therapies targeting basic defects in CF are considered the highest longevity of these children worldwide [10, 11]. In Bangladesh, genetic diagnosis of CF patients is still challenging, and diagnosis depends on the high level of clinical suspicion as well as supportive evidence. Knowing the clinico-epidemiological characteristics is therefore thought to be useful for clinicians to understand the natural history, disease process, sociodemographic pattern, and short-term outcome of these patient groups. With regard to the scarcity of information on epidemiological aspects of this disease in Bangladesh, this observational study was designed to summarize the clinic-epidemiological characteristics of pediatric cystic fibrosis attending Dhaka Sishu (children) Hospital, Bangladesh.

2. Patients And Methods

Patients and study settings:

Patients with CF living in Bangladesh and attending the CF clinic in Dhaka Sishu (children) Hospital (DSH), Dhaka, Bangladesh in the period February 2021 and October 2021 were selected for the study. Dhaka Sishu (children) Hospital is the largest tertiary level hospital that serves dedicated to children and deals thousands of cases each year. The hospital provides for various pediatric health problems. It operates a CF clinic equipped with a multidisciplinary team specialized in the management of CF. Hence, it receives referrals and admissions from nearby districts and cities. During the study period, a total of 181 suspected cases were examined and investigated. Finally, a total of 50 cases of CF (46 confirmed cases and 4 possible cases) were included in this study. Details about the patient selection are described in **supplementary figure 1**.

Diagnosis of the children: A total of 50 individuals aged less than 14 with a clinical diagnosis of CF were included in the study. Diagnosis was confirmed by characteristic symptoms of CF and/or a positive family history of CF and/or a positive sweat chloride test for two separate samples. A chloride concentration of more than and above 90 mmol/L in sweat was considered positive for CF, and 60-89 mmol/L was considered a possible case[12]. Patients were excluded if CF was ruled out in further follow-ups. SANASOL (SM-01) sweat analyzer (Country of origin: Sanasol Ltd. Hungary) was used to determine the total ion quality. As facilities for genetic testing are sparse in the country, we were able to conduct genetic studies for 2 children only. All patients were managed according to the hospital protocol and were observed up to discharge.

Clinical case management protocol:

This was prepared in line of therapeutic management. Treatment included counseling about the disease, airway clearance therapy, antibiotics both systemic and inhalational, anti-inflammatory agents, mucolytics, pancreatic enzyme replacement, calcium, multivitamins and nutritional support.

Data gathering:

Data were collected in a structured case record form. Demographic information was obtained from interviews with parents of children with CF. It included age of the child, gender, family history, and consanguinity of parents. Clinical information obtained from the children included the nutritional status of the child, clinical manifestation at the time of the interview, and laboratory investigations. All patients were subjected to thorough physical examination, and the findings were recorded in the case record form. Height and weight were measured for all children. Nutritional status was defined as underweight (<2 SD of weight for age), wasting (<2 SD for weight for height), and stunting (<2 SD of height for age) using WHO growth charts. Laboratory profiles and other investigations, such as complete blood count (CBC), random blood sugar (RBS), liver enzymes [serum alanine aminotransferase (ALT)], stool for occult blood, fat globules and occult parasites, chest radiograph, and echocardiography results, were also assessed. In addition, comorbidities of the children with CF were also recorded. The outcome was defined as 'alive' in cases of discharge from the hospital and 'died' in cases of in-hospital deaths. Data collection was performed by study research physicians under the supervision of the investigator team.

Ethics statement: Informed written consent was ensured before participation in the study and was obtained from parents or their legal representatives after disclosing the full purpose of the study. The institutional review board (IRB) of Bangladesh Institute of Child Health, Bangladesh [ethical approval no. BICH-ERC-5-2-21)] approved the study in 2021.

Statistical analyses:

Data were analyzed using SPSS Version 26. Descriptive statistics were used to describe the sociodemographic distribution, clinical profile and comorbidities of the admitted children. Chi-square tests, Fisher's exact tests, and Student's t tests were used as appropriate. A nonparametric test (Mann-Whitney U test) was used in the relevant case. Statistical significance was determined at $p \leq 0.05$.

Results:

The mean and median age of the 50 children included in this study was 39.70 months and 30 months, respectively. The age ranged from 6 to 120 months, and the majority were aged between >1 and 5 years (60%). Most of the children were male (66%) except the infants who were predominantly female (66.7% of infants). Of all, 57.14% of children had a family history of cystic fibrosis, 41.67% of children's parents had consanguinity of marriage, 86% were underweight, 54% had wasting and 86% had stunting. All these characteristics were statistically similar across age groups (Table 1). Out of all, 16% died, and 84% were

discharged after improvement (Figure 1). There was no significant difference between those who improved and those who died in relation to age, sex, family history, and nutritional status (**Supplementary Table 1**).

Table 1
Demographic characteristics, family history and nutritional status of children

Variable	Total (n=50)	≤1 years (n=9)	> 1 to 5 years (n=30)	> 5 years (n=11)	p- value
	n (%)	n(%)	n (%)	n (%)	
n (%)	50 (100)	9 (18)	30 (60)	11 (22)	
Age at diagnosis (Months)					
Mean ±SD	39.7 ±30.75	9.11 ±2.47	30.23 ±11.36	90.54 ±17.27	
Median (Min-Max)	30 (6 – 120)	9 (6 – 12)	30 (17 – 48)	84 (72 – 120)	
Sex					
Male	33 (66.00)	3 (33.33)	24 (80.00)	6 (54.55)	0.023
Female	17 (34.00)	6 (66.67)	6 (20.00)	5 (45.45)	
Family History of Cystic Fibrosis (n=49)					
Present	28 (57.14)	5 (55.56)	18 (60.00)	5 (50.00)	0.853
Absent	21 (42.86)	4 (44.44)	12 (40.00)	5 (50.00)	
Consanguinity of marriage between parents (n=36)					
Present	15 (41.67)	1 (14.29)	10 (47.62)	4 (50.00)	0.260
Absent	21 (58.33)	6 (85.71)	11 (52.38)	4 (50.00)	
Nutritional Status**					
Underweight					
Yes	43 (86.00)	6 (66.67)	26 (86.67)	11 (100.00)	0.100

p-value determined by Chi-square test where appropriate

* Nutritional status was defined as follows: Underweight (<2SD of weight for age), Wasting (<2SD for weight for height) and stunting (<2SD of height for age).

Variable	Total (n=50)	≤1 years (n=9)	> 1 to 5 years (n=30)	> 5 years (n=11)	p- value
No	7 (14.00)	3 (33.33)	4 (13.33)	0	
Wasting					
Yes	23 (46.00)	5 (55.56)	16 (53.33)	2 (18.18)	0.110
No	27 (54.00)	4 (44.44)	14 (46.67)	9 (81.82)	
Stunting					
Yes	43 (86.00)	6 (66.67)	26 (86.67)	11 (100.00)	0.100
No	7 (14.00)	3 (33.33)	4 (13.33)	0	
p-value determined by Chi-square test where appropriate					
* Nutritional status was defined as follows: Underweight (<2SD of weight for age), Wasting (<2SD for weight for height) and stunting (<2SD of height for age).					

The median duration of disease was 12 months (range 2 to 72 months). Cough and purulent sputum or hemoptysis was the most prevalent symptom being present in 100% of cases. Additionally, failure to thrive and bulky offensive stool were present in 98% and 86% of cases, respectively. The most frequent sign was malnutrition (94%), followed by short stature (72%), digital clubbing (64%), and bronchiectasis (40%). All the symptoms and signs were present in a similar proportion in all age groups except bronchiectasis which was significantly more frequent among the children age ≥ 5 years (Table 2). Additionally, all the symptoms including duration of disease were present in statistically similar proportion in both live and dead children except digital clubbing, bronchiectasis, pancreatic insufficiency, and abnormal liver function tests, which were present in a significantly higher proportion among those who died (Supplementary Table 2).

Table 2
Clinical characteristics of children with cystic fibrosis in relation to age category

Variable	Total (n=50)	≤1 years (n=9)	> 1 to 5 years (n=30)	> 5 years (n=11)	p- value
	n (%)	n(%)	n (%)	n (%)	
Disease Duration (Month)					
Median (Min-Max)	12 (2 – 72)	5.5 (3 – 9)	11 (2 – 32)	36 (12 – 72)	
Symptoms					
Respiratory Features					
Cough	50 (100)	9 (100)	30 (100)	11 (100)	NA
Purulent sputum or haemoptysis	50 (100)	9 (100)	30 (100)	11 (100)	NA
“Asthma” with chest infection	12 (24.49)	0(0.00)	7 (23.33)	5 (45.45)	0.073
Nasal Polyp	8 (16.67)	1 (14.29)	5 (16.67)	2 (18.18)	0.977
Chronic Sinusitis	5 (10.00)	0 (0.00)	2 (6.67)	3 (27.27)	0.081
Gastrointestinal Features					
Failure to thrive	49 (98.00)	8 (88.89)	30 (100.00)	11 (100.00)	0.098
Bulky offensive stools	43 (86.00)	7 (77.78)	26 (86.67)	10 (90.91)	0.692
Meconium Ileus	5 (10.00)	2 (22.22)	2 (6.67)	1 (9.09)	0.392
Prolonged neonatal jaundice	4 (8.00)	1 (11.11)	3 (10.00)	0 (0.00)	0.539
Rectal prolapse	1 (2.00)	0 (0.00)	1 (3.33)	0 (0.00)	0.712
Constipation	1 (2.00)	0 (0.00)	1 (3.33)	0 (0.00)	0.712
Signs					
Malnutrition	47 (94.00)	7 (77.78)	29 (96.67)	11 (100.00)	0.071
Short stature	36 (72.00)	7 (77.78)	21 (70.00)	8 (72.73)	0.900
Digital clubbing	32 (64.00)	4 (44.44)	18 (60.00)	10 (90.91)	0.076
Bronchiectasis	20 (40.00)	1 (11.11)	9 (30.00)	10 (90.91)	<0.001
Edema	12 (24.00)	3 (33.33)	5 (16.67)	4 (36.36)	0.327

p-value determined by Chi-square test where appropriate

Variable	Total (n=50)	<=1 years (n=9)	> 1 to 5 years (n=30)	> 5 years (n=11)	p-value
Pancreatic insufficiency	5 (10.00)	0 (0.00)	3 (10.00)	2 (18.18)	0.403
Abnormal liver function test	7 (14.00)	1 (11.11)	3 (10.00)	3 (27.27)	0.355
Sinus disease	5 (10.00)	1 (11.11)	2 (6.67)	2 (18.18)	0.549
p-value determined by Chi-square test where appropriate					

The most common complication among children was pulmonary hypertension (48%). In addition, asthma, meconium ileus, allergic bronchopulmonary aspergillosis, and neonatal hepatitis syndrome were present in 12%, 6.52%, 2%, and 2%, respectively. There was no age-related difference in the distribution of complications (Table 3). However, pulmonary hypertension and allergic bronchopulmonary aspergillosis were present in a statistically significantly higher proportion in children who died than in those who were alive (Supplementary Table 3).

Table 3
Complications of children with cystic fibrosis in relation to age category

Variable	Total (n=50)	<=1 years (n=9)	> 1 to 5 years (n=30)	> 5 years (n=11)	p-value
	n (%)	n (%)	n (%)	n (%)	
Pulmonary Hypertension	24 (48.00)	4 (44.44)	14 (46.67)	6 (54.55)	0.880
Asthma	6 (12.00)	0 (0.00)	3 (10.00)	3 (27.27)	0.152
Meconium Ileus	3 (6.52)	1 (11.11)	2 (7.69)	0 (0.00)	0.566
Allergic bronchopulmonary aspergillosis	1 (2.00)	0 (0.00)	1 (3.33)	0 (0.00)	0.712
Neonatal Hepatitis Syndrome	1 (2.00)	0 (0.00)	1 (3.33)	0 (0.00)	0.712
p-value determined by Chi-square test					

The median hemoglobin level, WBC count, platelet count, RBS and ALT were 10.7 g/dl, 13.85 x 10³/mm³, 3.00 x 10⁶/mm³, 4.7 mmol/l and 55 u/l, respectively. On chest X-ray, 66% had bilateral patchy opacity, 40% hyperinflation of the lung, 16% had consolidation or inhomogeneous opacity, and 10% had a honeycomb appearance. Older children were significantly more likely to have lower median lymphocyte count than infants (Table 4). In addition, children who died had significantly higher ALT levels and a

significantly higher frequency of honeycomb appearance on chest X-ray than their counterparts ($p=0.005$) (Supplementary Table 4).

Table 4
Investigation findings of children with cystic fibrosis in relation to age category

Variable	Total (n=50)	≤ 1 (n=9)	> 1 to 5 (n=30)	> 5 (n=11)	p-value*
Sweat Chloride Test (meq/l) (n=49)					
60 – 89	4 (8.00)	1 (11.11)	2 (6.67)	1 (9.09)	0.901
≥90	46 (92.00)	8 (88.89)	28 (93.33)	10 (90.91)	
Hemoglobin (g/dl)	10.70 (7.10 – 17.40)	9.80 (7.10 – 17.40)	10.95 (7.90 – 13.90)	10.50 (9.10 – 13.90)	0.3617
WBC (tc) (x10 ³ /mm ³)	13.85 (1.70 – 48.20)	1.50 (7.60 – 4.82)	14.65 (5.50 – 29.00)	9.70 (1.70 – 20.50)	0.107
Neutrophil (%)	54.50 (21.00 – 86.00)	37.00 (21.00 – 72.00)	58.50 (27.00 – 86.00)	55.00 (25.00 – 78.00)	0.057
Lymphocyte (%)	44.00 (10.00 – 71.00)	56.00 (32.00 – 71.00)	38.00 (10.00 – 65.00)	45.00 (16.00 – 68.00)	0.016
Platelet (plt) (x 10 ⁶ /mm ³)	3.00 (0.47 – 6.13)	201 (112 – 441)	318.5 (470 – 613)	212 (105– 574)	0.243
Random blood sugar (rbs) (mmol/l)	4.70 (3.10 – 6.70)	4.30 (3.20 – 6.10)	4.70 (3.10 – 36.00)	4.90 (3.30 – 6.70)	0.353
Serum ALT (sgpt) (U/L)	55.00 (17.00 – 212.00)	47.00 (25.00 – 88.00)	45.00 (17.00 – 100.00)	72.00 (23.00 – 212.00)	0.098
Stool for fat (globules/hpf)					
Not done	28 (56.00)	7 (77.78)	15 (50.00)	6 (54.55)	0.136
≤ 200	8 (16.00)	2 (22.22)	6 (20.00)	0 (00.00)	
> 200	14 (28.00)	0 (00.00)	9 (30.00)	5 (45.45)	
Chest X-ray					
Bilateral patchy opacity	33 (66.00)	7 (77.78)	20 (66.67)	6 (54.55)	0.547
Hyperinflation of lung	20 (40.00)	6 (66.67)	13 (43.33)	1 (9.09)	0.028
Consolidation or inhomogeneous opacity	8 (16.00)	2 (22.22)	4 (13.33)	2 (18.88)	0.796
Honeycomb appearance	5 (10.00)	0 (0.00)	2 (6.67)	3 (27.27)	0.081

*p-value determined by Kruskal Wallis test and Chi-square test where appropriate; Data was expressed as median (min-max) or n(%) where appropriate

Variable	Total (n=50)	<= 1 (n=9)	> 1 to 5 (n=30)	> 5 (n=11)	p-value*
Hypoproteinemia	37 (74.00)	7 (77.78)	20 (66.67)	10 (90.91)	0.281
*p-value determined by Kruskal Wallis test and Chi-square test where appropriate; Data was expressed as median (min-max) or n(%) where appropriate					

Discussion:

CF was a relatively overlooked problem in Bangladesh. Only recently was a multicenter study of 94 cases over a period of 17 years between 2000 and 2017 published by Kabir *et al* [13] in 2020. Given the scarcity of information regarding children with CF in the country, it was reasonable to continue the exploration of demographic and clinical features of CF patients. Additionally, an examination of the patients' characteristics across outcomes would identify important conditions to be addressed during management. Hence, this study was aimed.

The average age at diagnosis of our participants was lower than that found by Kabir *et al* [13] in Bangladesh, Kabra *et al* [15] in India, and Aziz *et al* [16] in Pakistan. Increased availability of diagnostic facilities might have lowered the age of diagnosis of CF. We found a slightly higher proportion of males, in conformity with previous studies [13, 15, 16]. However, unlike previous studies [17], we did not note any increased risk of case fatality among female patients.

Out of 50 children with CF included in the study, 16% died. This is higher than the previous finding by Kabir *et al* [13], who reported 11 deaths out of 95 patients (case fatality 11.5%). Additionally, this figure of childhood case fatality is much higher than in Western countries equipped with better management resources [14].

As an autosomal recessive genetic disorder [3], a family history of CF and consanguinity of marriage between parents are common findings in CF patients. We noted a family history in nearly three-fifths (57.1%) of patients and consanguinity of marriage in more than two-fifths (41.7%). In contrast, consanguinity was found in 22%, 55.8%, and 15% of cases by Kabir *et al* [13], Aziz *et al* [16], and Kabra *et al* [15], respectively. These differences in distribution agree with the global distribution of consanguinity, where an important cluster of countries shows a high level of consanguinity and includes mostly Muslim majority areas [18]. However, the distribution might vary due to other factors, including religion, race, ethnicity, and sociocultural factors.

We noted a very high prevalence of malnutrition in the form of underweight, stunting, and wasting among our children with CF, which conforms with other studies [15, 16]. All age groups and both alive and dead children shared a statistically similar proportion of malnutrition. Malnutrition is common in cystic fibrosis, and the cause of growth failure and malnutrition is multifactorial, including chronic inflammation [3].

The most frequent clinical features were cough with purulent sputum or hemoptysis and failure to thrive among the study participants. Additionally, malnutrition, short stature, digital clubbing, and bronchiectasis were predominant signs. Cough occurs mainly due to repeated infection of the airway. Hence, recurrent respiratory infections and failure to thrive are the most commonly reported symptoms in studies involving CF[15, 16, 19–21]. Children with CF frequently pass bulky offensive stools due to fat malabsorption from the gut, and malnutrition occurs due to inadequate absorption of proteins, fats, and fat-soluble vitamins because of pancreatic insufficiency [22]. All the symptoms occur across all age groups. Interestingly, however, we noted an association of case fatality with the presence of digital clubbing, bronchiectasis, pulmonary hypertension, allergic bronchopulmonary aspergillosis, pancreatic insufficiency, abnormal liver tests, and honeycomb appearance on chest X-ray. All these features are suggestive of advanced disease [23]. In particular, the presence of bronchiectasis and honeycombing indicates underlying chronic inflammation and repeated infection. Management of pancreatic insufficiency requires multidisciplinary, carefully tailored strategies[3], which are often not possible in resource-poor settings. Hence, a combination of explored and unexplored factors might be responsible for premature deaths in CF among children in our setting.

Our study was limited by the fact that it was a single-center study with a small sample of cases. Genetic studies were not available for most of the patients due to economic problems or a lack of adequate facilities. Long-term follow-up of the patients was beyond the scope of the study. However, the study presented a detailed examination of sociodemographic and clinical features of children with CF in the country with a comparison across different outcomes, which will aid in the diagnosis and management of CF cases.

Conclusion

Cough, purulent sputum, and bulky offensive were the prominent presenting symptoms of children with CF. Failure to thrive is a global feature. Laboratory, radiographic and echocardiographic assessments support several abnormalities linked with the disease. To yield more reliable epidemiological information of these patients, a single prospective nationally representative database is therefore warranted.

Declarations

- **Ethics approval and consent to participate:** The study protocol was approved by the institutional review board (IRB) of Bangladesh Institute of Child Health, Bangladesh [ethical approval no. BICH-ERC-5-2-21)]
- **Consent for publication:** all authors approved the final version for publication
- **Availability of data and materials:** Data and material are available from the corresponding authors and could be shared based on reasonable request.
- **Competing interests:** None to declare
- **Funding:** No external fund was used to conduct the study.

- **Authors' contributions:**

- The conception and design: PKS, NA, MASK and MJH
- Data acquisition and data collection: PKS, NA, ST, MK, JA, KAZ,TF, MMH, MJA
- Data analysis was done by MASK and MJH
- Interpretation of the result: PKS, NA, ST, MK, JA, KAZ,TF, MMH, MJA, MASK and MJH
- Project administration: PKA,NA,ST,MJA,TF
- First draft of the manuscript: PKS, NA, MASK and MJH
- Review of the draft: PKS, NA, ST, MK, JA, KAZ,TF, MMH, MJA, MASK and MJH
- Final approval: PKS, NA, ST, MK, JA, KAZ,TF, MMH, MJA, MASK and MJH

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Figures

Figure 1

Outcome of children with cystic fibrosis (n=50)

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