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Insight into clinical, laboratory, and GIT ultrasound diagnostic findings of cystic fibrosis in pediatrics

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Abstract

Background: Cystic fibrosis (CF) is a multisystem disorder. Gastrointestinal tract (GIT) involvement presently requires medical attention, and this improves the survival rate of patients with CF. GIT imaging has an essential role in the early detection of GIT affection. This study aimed to quantify the abdominal symptoms and their relationship to clinical findings, abdominal ultrasound scoring system, and laboratory parameters, correlating GIT manifestation with ultrasound diagnostic findings.

Methods: This was a cross-sectional study that included 60 patients diagnosed with CF based on clinical manifestations and confirmed by a positive sweat chloride test ≥ 60 mmol/L and/or genetic analysis (CFTR gene mutation; a copy from each parent) in the CF clinic in the Children's Hospital, in a period of 12 months.

Results: Recurrent abdominal pain (RAP) was the most common GIT manifestation, followed by abdominal distension and steatorrhea. Ultrasonography (US) showed that the most frequent findings were pancreatic lipomatosis in 16 patients (26.7%), the next common finding was heterogeneous coarse hepatic parenchyma in 14 patients (23.3%), while the least finding was the thickened bowel walls in 2 patients (3.3%). Abdominal US scoring revealed that the highest burden of GIT symptoms was clearly associated with pancreatic lipomatosis and liver steatosis with the highest score (6/7) ($p = 0.048$), while bowel wall thickness (BWT) had the lowest score (3/7) (Table 4).

Conclusion: This study reveals that abdominal US is a non-invasive investigation that helps in the early detection of GIT involvement in CF. RAP is a common GIT manifestation and may reflect a major pathology. Moreover, a significant relationship was detected between RAP and pancreatic cystosis and lipomatosis. Therefore, the study also highlights the importance of US as a routine non-invasive follow-up tool for patients with CF and suggests close monitoring of patients with CF by abdominal US performed every 6 to 12 months.

Keywords: Abdominal symptoms, Abdominal ultrasound, Cystic fibrosis

Background

Cystic fibrosis (CF) is a genetic disease resulting from abnormalities in the CF transmembrane conductance regulator (CFTR), a chloride channel found in the cells lining the lungs, intestines, pancreatic ducts, sweat glands, and reproductive organs. The most common clinical manifestations are pancreatic insufficiency leading to calorie malabsorption, and lung affection caused by mucus retention, infection, and inflammation [1].

Abdominal involvement in CF is not completely understood and still gets less scientific attention in relation to pulmonary involvement [2].

Ultrasonography (US) has a high impact for detecting abdominal pathologies noninvasively and without exposure to radiation. It allows static and dynamic assessment

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of pathologies such as pancreatic cystosis and lipomatosis, liver changes, and bowel wall thickness [2].

There are few reports regarding the correlation between the GIT symptoms and US findings in the literature. This study aimed to highlight the most frequent abdominal symptoms and prevalence of these symptoms with each US pathology, correlating GIT manifestation with ultrasound diagnostic findings using the ultrasound scoring system.

Methods

This was a cross-sectional study that included 60 patients diagnosed with CF based on clinical manifestations and confirmed by a positive sweat chloride test ≥ 60 mmol/L and/or genetic analysis (CFTR gene mutation; a copy from each parent) for patients with positive clinical manifestations but negative sweat chloride tested for delta F508 by genetic analysis in the CF clinic in the Children's Hospital, in a period of 12 months (Table 1).

Children with CF aged up to 18 years were included in the study. The cohort included only confirmed CF patients by history, clinical manifestations, positive sweat chloride, and/or genetic analysis. The diagnosis confirmed by; one diagnostic modality is acceptable when the patient has clinical manifestations and 2 positive sweat chloride tests or clinical manifestations and genetic analysis positive.

The study was approved by the Institutional Ethics Committee of the hospital (I-171015), and informed consent was obtained from the study subjects and/or their legal guardians before participating.

The patients were subjected to the following:

- Full medical history, including age, sex, age of onset of symptoms and date of CF diagnosis, and chest symptoms (chronic cough and sputum production). GIT manifestation (abdominal distension, vomiting, steatorrhoea (frequent, bulky, foul-smelling, greasy stools), failure to thrive, abdominal pain, GIT bleeding, and delayed passage of meconium). Family history of consanguinity and similar conditions. Past history of delayed passage of meconium and prolonged jaundice and duration of previous hospital admission and its frequency.
- Physical examination: measurements of height and weight in all patients with CF were conducted and classified as < 5th percentile and from the 5th to 95th percentile according to the Center of Disease Control growth charts. Vital signs monitoring and chest and abdominal examination were performed.
- Laboratory investigations: complete blood count with a differential count. Liver function tests (LFTs) (ALT, AST, GGT, and bilirubin; total and direct) and stool analysis were done for all patients to check for steatorrhea (presence of fat globules) and parasitic infestations.
- Radiological investigation: measurement of US abnormalities and US examinations were performed at a single center using a US scanner (TOSHIBA Xario 100) with a 3.5-MHz abdominal probe under standardized conditions.
- The abdominal US findings included an assessment of 13 parameters:
  - *Bowel wall thickness (BWT)* was measured in both a longitudinal and a transverse section. The measurement was taken from the central hyperechoic line of the lumen (which is the interface between the content of the lumen and the mucosa) to the outer hyperechoic margin of the wall (which is the serosa). BWT was considered normal up to 3 mm [3].
  - *Mesenteric lymph nodes* were considered enlarged if greater than 10 mm in the long axis and larger than 5 mm in the shorter axis [3].
  - *Intussusception* which is the invagination of a proximal segment of the intestine into an adjacent distal segment. On the axial US section, it appears as a mass with multiple concentric rings (doughnut signs) [3].

Table 1 Demographic data of the study population

Variable		
	Mean	**SD**
Age (years)	6.26	3.65
Age of onset of symptoms by months	2.21	2.1
Age of cystic fibrosis diagnosis by months	14.15	32.35
Pancreatic enzyme units of Creon/kg	3132	1220
Variable	Number	Percentage (%)
Sex		
Male	20	33
Female	40	67
Positive consanguinity	20	33
Family history of similar condition	14	23
Weight		
< 5th percentile	42	70%
5th–95th percentile	18	30%
Height		
< 5th percentile	36	60%
5th–95th percentile	24	40%

- *Appendiceal thickening* was considered if its diameter of more than 6 mm with or without an appendiceal wall thicker than 2 mm.
- *Free fluid* within the peritoneal cavity.
- *Pancreatic cystosis* was defined as rounded or oval cystic anechoic structures if sizes were greater than 1 cm (representing macroscopic cysts) [4].
- *Pancreatic lipomatosis* was defined when pancreatic echogenicity was higher than the liver.
- *Cholecystolithiasis* was defined as gall bladder with typical acoustic shadow inside and micro-gallbladder if less than 2–3 cm in length and 0.5–1.5 cm in width [5].
- *Coarseness of the hepatic parenchyma* (heterogenecity), nodularity of the liver edge, and periportal fibrosis (if increased periportal echoes).
- *Liver steatosis* if increased echogenicity compared to the renal parenchyma, vascular blurring, and deep attenuation of the US signal [6].
- *Hepatomegaly and splenomegaly* were considered if larger than the upper limits according to age.
- *A radiological score* was calculated by correlating GIT manifestation with US findings. This score represents the number of GIT symptoms (7 GIT symptoms) (Table 2) which were found with each US finding.

Statistical methods

Data were subjected to computer-assisted statistical analysis using Statistical Package for Social Sciences (SPSS) version 18. Nominal data were expressed as frequency and percentage and compared using chi-square test. Numerical data were expressed as mean + / − standard deviation and compared using *t*-test. Nonparametric data were expressed as median, "interquartile range" and compared using Mann–Whitney *U* test. Associations between numerical variables were studied using Pearson's correlation. *P*-values < 0.05 were considered significant. Charts and graphs were prepared using Excel or SPSS programs.

Table 2 Frequency of abdominal symptoms

Variable	Number	%
Vomiting	24	40
Steatorrhea	24	40
FTT	30	50
Recurrent abdominal pain	52	86.7
Delayed passage of meconium	16	26.7
Abdominal distension	46	77
GIT bleeding	2	3.3

Results

Our study included 60 children with CF, consisting of 40 boys (67%) and 20 girls (33%), with mean age of 6.26 ± 3.65 years. Positive consanguinity was detected in 20 patients (33.3%), and positive family history of CF was detected in 14 patients (23.3%) (Table 1).

Chronic cough with sputum production was the main chest complaint (93%), followed by failure to thrive in 50%, vomiting in 40%, and steatorrhoea in 40%, while recurrent abdominal pain (RAP) was the most common GIT complaint (86.7%), followed by abdominal distension in77%, delayed passage of meconium in 26.7%, and GIT bleeding in 3.3% (Table 2).

LFTs were performed with a mean ALT level of 63 ± 105 U/L, mean AST level of 58 ± 83 mg/dL, mean GGT level of 85.67 ± 129.32 U/L, mean total bilirubin level of 0.55 ± 0.75 mg/dL, and mean direct bilirubin level of 0.20 ± 0.46 mg/dL (Table 3).

Ultrasonography (US) showed that the most frequent findings were pancreatic lipomatosis in 16 patients (26.7%), heterogeneous coarse hepatic parenchyma in 14 patients (23.3%), micro-gallbladder in 12 patients (20%), both pancreatic cystosis and liver steatosis in 10 patients (16.7%), periportal fibrosis in 8 patients (13.3%), hepatomegaly in 6 patients (10%), and both cholecystolitheasis and nodularity of liver edge in 4 patients (6.7%), and the least finding was the thickened bowel walls in 2 patients (3.3%). Some US abnormalities detected in the included patients with CF are shown in Figs. 1, 2, and 3.

A statistically significant relationship was found between RAP and each of pancreatic cystosis and pancreatic lipomatosis detected by US with (*P*-values, 0.009 and 0.048, respectively) (Fig. 3). However, no significant relationship was detected between pancreatic enzyme dose and US finding apart from pancreatic cystosis with near significant value (*P*-value, 0.06), which may be due to the small sample size.

Highest burden of GI symptoms was clearly associated with pancreatic lipomatosis and liver steatosis with the highest score (6/7) ($p = 0.048$), while BWT had the lowest score (3/7) (Table 4).

Discussion

Abdominal symptoms are a hallmark of CF. However, their relation with morphological abnormalities of various abdominal organs is still inadequately recognized [2].

Dysfunction of CFTR in the pancreatic ducts, biliary ducts, and intestinal epithelia results in viscous acidic secretions, leading to lumen obstruction and impaired digestion [7].

Table 3 Laboratory parameters of the studied patients

Variable	Mean (± SD)	Median (range)
Complete blood count		
Hemoglobin	11.34 (± 1.33)	11.3 (8.4–14.3)
Hematocrit	34.12 (± 3.8)	34.85 (25–42)
White blood cells	11.44 (± 4.3)	10.8 (3–16)
Platelets	370.23 (± 145)	365 (140–731)
Liver function tests		
ALT	63.08 (± 105.28)	35.5 (12–588)
AST	58.97 (± 83)	38 (19–472)
GGT	85.67 (± 129.32)	45 (12–521)
Bilirubin, total	0.55 (± 0.75)	0.35 (0.1–4.1)
Bilirubin, direct	0.20 (± 0.46)	0.1 (0–2.4)

Abdominal sonography has a high value for detecting abdominal pathologies non-invasively and without exposition to radiation. It is used commonly in diagnostic evaluation and can detect abnormalities of the pancreas, liver, gallbladder, spleen, and bowel. Knowledge of these manifestations is essential in the evaluation of the extent of CF as well as the determination of treatment requirements and effectiveness in these patients [8].

In our study, 50% of patients had failure to thrive (FTT) and 70% of patients were under the 5th percentile for body weight, showing that nutritional failure in patients with CF is a common presentation that needs close follow-up. Similar to our study, Kawoosa et al. detected FTT in 94% of patients in their study in children from Jammu and Kashmir [9].

In the current study, US showed that the most frequent findings were pancreatic lipomatosis in 16 patients (26.7%), heterogeneous coarse hepatic parenchyma in 14 patients (23.3%), micro-gallbladder in 12 patients (20%), both pancreatic cystosis and liver steatosis in 10 patients (16.7%), periportal fibrosis in 8 patients (13.3%), hepatomegaly in 6 patients (10%), and both cholecystolithiasis and nodularity of liver edge in 4 patients (6.7%), and the least finding was the thickened bowel walls 2 patients (3.3%). A study conducted by Tabori et al. (2017) reported that the most frequent abdominal US findings were in order pancreatic lipomatosis (88%), liver steatosis (37%), hepatomegaly (31%), BWT (23%), and coarse hepatic parenchyma (22%) with the least finding was intussusception (2%).

In this study, intussusception was not detected in any patient. Also, a study conducted by Nandi et al. reported that intussusceptions developed in 1–3% of cases of CF, which could be the result of improved management of these patients [10]. Another study by Colombo et al. agreed with our result, in which 1% of patients with CF had a history of intussusceptions and most of them were

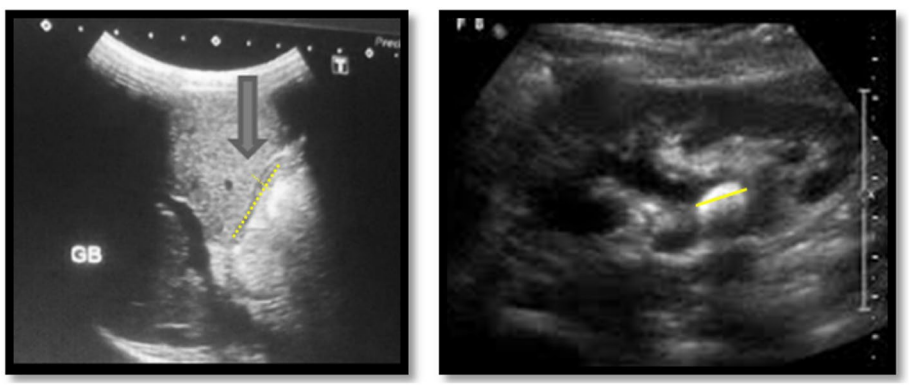

Fig. 1 A child known to have cystic fibrosis. He was complaining of chronic cough and recurrent abdominal pain. His labs are as follows: ALT, 19; AST, 24; Na, 128; K, 3.5; and random blood glucose, 90. Ultrasound of the abdomen shows heterogeneous liver parenchyma but with normal size, micro-gall bladder (arrow) measuring about 0.4 × 1.5 cm, right renal calculus measuring about 9 mm with mild back pressure changes

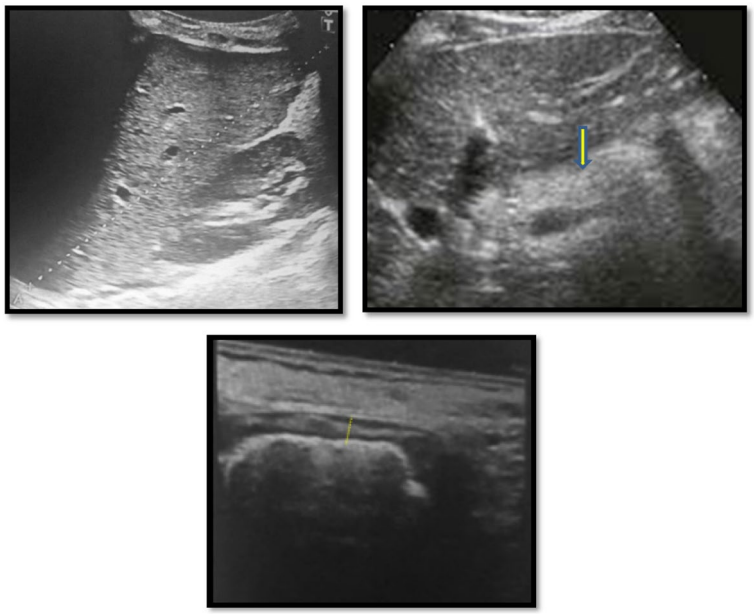

Fig. 2 A child known to have cystic fibrosis. She was complaining of chronic cough, recurrent abdominal pain, failure to thrive, and steatorrhea improving on pancreatic enzyme replacement therapy. Her labs are as follows: ALT, 19; AST, 25; Na, 138; K, 3.6; and random blood glucose, 130. Ultrasound of the abdomen shows heterogeneous liver parenchyma with hepatomegaly measuring about 14.7 cm, increased pancreatic echogenicity (pancreatic lipomatosis, arrow), and increased small bowel wall thickening measuring up to 0.5 cm

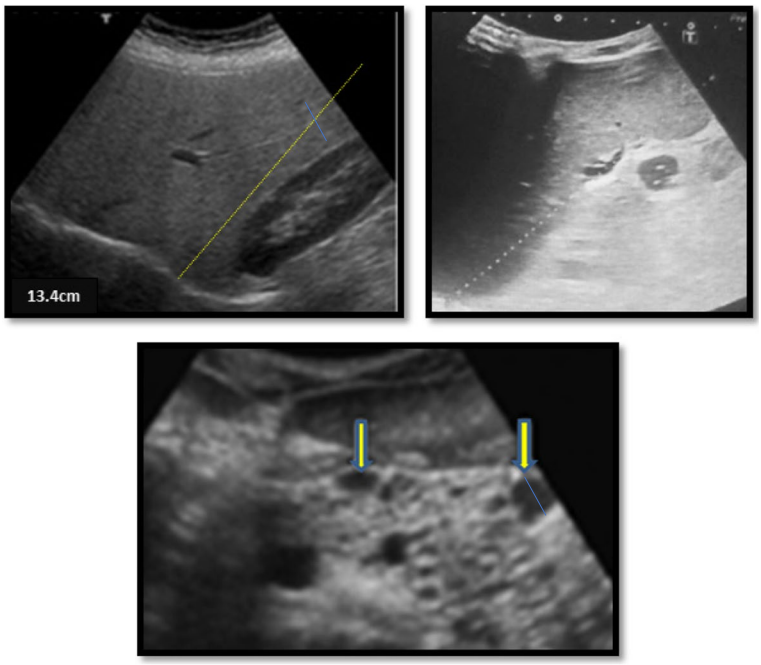

Fig. 3 A child known to have cystic fibrosis. He was complaining of chronic cough, vomiting, recurrent abdominal pain, and steatorrhea improving on pancreatic enzyme replacement therapy. His labs are as follows: ALT, 15; AST, 38; Na, 139; K, 4.1; and random blood glucose, 92. Ultrasound of the abdomen shows fatty echogenic liver parenchyma with hepatomegaly measuring about 13.4 cm, splenomegaly measuring 12.9 cm, and increased pancreatic echogenicity with multiple variable-sized cysts measuring up to 20 mm (pancreatic lipomatosis and cystosis, arrow)

Table 4 Frequencies (score) of detected abnormalities in abdominal ultrasound and associated abdominal symptoms

Pathologies detected by abdominal US	*N* (%)	Number of abdominal symptoms associated with each pathology
Bowel wall thickness (BWT)	2 (3.3%)	3/7
Pancreatic cystosis	10 (16.7%)	5/7
Pancreatic lipomatosis	16 (26.7%)	6/7
Cholecystolithiasis	4 (6.7%)	5/7
Microgallbladder	12 (20%)	4/7
Coarseness of the hepatic parenchyma	14 (23.3%)	5/7
Nodularity of the liver edge	4 (6.7%)	4/7
Periportal fibrosis	8 (13.3%)	5/7
Liver steatosis	10 (16.7%)	6/7
Hepatomegaly	6 (10%)	5/7

asymptomatic [11]. In contrast to our study, Fraquelli et al. in a prospective study including 70 CF patients and 45 controls who underwent abdominal US, in which 17% of patients showed intussusception, found that patients with CF had a higher frequency of bowel US abnormalities than controls [12].

US did not detect appendiceal thickening for our patients with CF. On the contrary, a study conducted in 2004 on 31 children detected enlargement of the appendiceal diameter in most of the included children, although the patients were asymptomatic, which show that the appendiceal diameter alone may not be a factor for diagnosing appendicitis in patients with CF [13].

In the present study, there was no correlation between US finding and LFTs. This was in line with Lewindon et al.'s study, which reported that LFTs are largely nonspecific in CF and considered inaccurate as a marker of severity or progression of CFLD, as patients with liver cirrhosis can have normal LFTs [14].

Currently, however, best practice guidelines recommend screening for CFLD using basic laboratory markers (LFTs, platelets, and international normalized ratio) and abdominal US. Additional imaging with CT or MRI is recommended if liver lesions or biliary tract involvement is detected on US without sufficient clarity for diagnosis [15].

In our study, RAP was the most common abdominal symptom among patients as 87% of the patients complained of RAP and 77% of patients complained of abdominal distension. Similarly, a recent survey of pain in patients throughout their lives by Sermet-Gaudelus et al. detected a high incidence of untreated pain; they included 73 children, and 59% of them reported at least one episode of pain in a month, with predominant abdominal location (60%) and 15% reported school absence and one-third of the cohort stated a negative impact on their family life [16].

Moreover, a prospective study involving children and adolescents with CF with mild severity revealed that the prevalence of RAP was as low as 6%, which was hypothesized that the low incidence of RAP in their study because of using Apley's criteria, which described RAP as at least three attacks of pain, severe enough to disturb one's activities, over at least period of three months, with attacks persisting in the year preceding the examination, which may result in exclusion of many children from the study with less severe pain [17].

In another study by Jeffrey et al. including 46 children, a self-report questionnaire was used to evaluate characteristics of chronic disease-related pain, in which 46% of the sample described the pain occurring at least once per week. Most children described their pain intensity as mild and of short duration. However, a small subgroup of children stated long-lasting and moderately intense pain [18].

In this study, the highest burden of GI symptoms was clearly associated with pancreatic lipomatosis and liver steatosis with highest score (6/7) ($p=0.048$) (Table 4). A significant relationship was detected between pancreatic cystosis and pancreatic lipomatosis by US and RAP with (*P*-values, 0.009 and 0.048, respectively) (Fig. 3). Prominent US findings such as pancreatic cystosis, which was detected in 10 patients (16.7%), with cyst lesions measuring up to 20 mm did not significantly contribute to the burden of abdominal symptoms in these patients with a score (5/7); however, this pathology may cause symptoms later on.

DeGruchy et al. presented a single case report of a 9-year-old girl with CF presenting with radiating abdominal pain and abdominal US showed replacement of the pancreatic head region by a large echoic cystic mass and

CT confirmed multiple simple macrocysts, which indicated that pancreatic cystosis might subsequently cause symptoms, for example, when further growth of cysts compresses adjacent structures [19].

In line with our study, Tabori et al. found that patients with pancreatic lipomatosis discovered by abdominal US showed a higher abdominal pain frequency, duration, and intensity than those without pancreatic lipomatosis, but they did not agree with our results on the relationship between pancreatic cystosis and RAP as they found that pancreatic cystosis, which was detected in 6% patients, with cyst lesions measuring up to 40 mm, did not contribute significantly to the burden of abdominal symptoms in these patients.

In the recent study, the least finding was the thickened bowel walls in 2 patients (3.3%), with BWT having the lowest score (3/7). In concomitant with Tabori et al. (2017), they revealed that thickened bowel walls, as detected in (23%) in their study, were not significantly correlated with an increased burden of GI symptoms. Therefore, the etiology of bowel wall thickening in CF patients is not fully understood until now. An intestinal wall inflammation, and possibly to dysbiosis, has been encountered and, in the long run, it could lead to submucosal fibrosis [2].

The current study, no relationship was found between pancreatic enzyme replacement therapy (PERT) and US findings. Moreover, a study including patients with CF of all ages attending at the Jena University Hospital CF Center did not detect a correlation between pancreatic enzyme replacement and US abnormalities [2].

PERT is thought to be required to improve weight gain, prevent malnutrition, prevent deficiency of fat-soluble vitamins and essential fatty acids, and control abdominal symptoms of steatorrhoea [20].

Conclusion

Abdominal ultrasound may help in the early detection of GIT involvement in CF. RAP is a common GIT manifestation and may reflect a major pathology. Moreover, a significant relationship was detected between RAP, pancreatic cystosis, and lipomatosis, revealing the importance of US as a follow-up tool for patients with CF. This study suggests that close monitoring of patients with CF by abdominal US examination as a routine non-invasive follow-up investigation performed every 6 to 12 months.

Abbreviations

CF: Cystic fibrosis; GIT: Gastrointestinal tract; RAP: Recurrent abdominal pain; US: Ultrasonography; CFTR: CF transmembrane conductance regulator; LFTs: Liver function tests; BWT: Bowel wall thickness; SPSS: Statistical Package for Social Sciences; FTT: Failure to thrive; PERT: Pancreatic enzyme replacement therapy.

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Authors' contributions

All authors have read and approved the manuscript. Study concept: R.I., D.H., M.M., and M.H. Study design: M.M. and R.I. Data acquisition: R.I., M.H., and D.H. Data analysis and interpretation: R.I. and D.H. Statistical analysis: M.M. and R.I. Manuscript preparation: R.I., M.H., and D.H. Manuscript editing: R.I. and D.H. Manuscript reviewing: R.I. and D.H.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of Abu-Elrich Children University Hospital (I-171015), and informed consent was obtained from the participants' legal guardians before participating.

Consent for publication

A written consent was obtained from the participants' legal guardians for publication.

Competing interests

The authors declare that they have no competing interests.

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