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The impact of probiotics on pulmonary, gastrointestinal, and growth outcomes in pediatric cystic fibrosis: a randomized controlled trial

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Abstract

Objective Cystic fibrosis (CF) is a fatal hereditary disorder that leads to respiratory infections and gastrointestinal inflammation with possible association with intestinal dysbiosis. The present study was conducted with the aim of investigating the effects of probiotic consumption in improving pulmonary, gastrointestinal, and growth symptoms in patients with CF.

Materials and methods In this double-blind randomized clinical trial, 110 CF patients were examined. Patients were divided into two equal groups of 55 subjects. Patients in the probiotic group consumed Lactobacillus reuteri at the rate of 10^8 CFU/d for one month, and the control group received a placebo. Then, pulmonary, gastrointestinal, and growth-related outcomes as well as quality of life were assessed after one month of intervention as well as at three-month follow-up.

Results The results of our study showed that in both intervention and control groups, weight increases significantly after 12 weeks ($P=0.01$). However, no remarkable difference was reported between the two groups after 12 weeks ($P=0.09$). In addition, no significant changes were observed between the two groups after 4 and 12 weeks regarding BMI and FEV1. Based on the findings, the score of the CFQ questionnaire in the intervention group increased significantly in the 4th and 12th week. No significant differences were observed between the two groups in terms of factors related to lung function or exacerbations after 12 weeks.The only notable effect reported was related to pain attacks in the probiotic group compared to the placebo group after 4 weeks ($P=0.02$).

Conclusion In general, treatment with probiotics improved the quality of life in patients with CF. However, no significant effect was observed on pulmonary, gastrointestinal, and growth-related outcomes.

Trial registration This study was retrospectively registered IRCT registration number: IRCT20240105060622N1 (Registration date: 2024-08-16).

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Keywords Cystic fibrosis, Lactobacillus reuteri, Probiotics, Pulmonary, Gastrointestinal, Children

Introduction

Cystic fibrosis (CF) results from a genetic condition that causes a lack or shortage of functional cystic fibrosis trans-membrane regulator (CFTR) proteins resulting from mutations in the CFTR gene, which encodes an ion channel critical for chloride transport and epithelial hydration at the apical membrane of epithelial cells in various body systems [1]. This dysfunction results in the accumulation of thick mucus, particularly in the respiratory and gastrointestinal tracts, causing chronic infections, inflammation, and multisystem complications. Pulmonary inflammation and infection are hallmark features of CF, which starts in early childhood and results in respiratory failure, leading to progressive respiratory decline and early mortality in these patients [2]. Most children with CF experience colonization by pathogens like *Pseudomonas aeruginosa*, contributing to frequent pulmonary exacerbations and declining lung function. Gastrointestinal manifestations, including exocrine pancreatic insufficiency, malabsorption, and intestinal dysmotility, are common and further compromise patients' growth and nutrition [3, 4]. Gut dysbiosis, a disruption in the gut microbiota, is another significant feature of CF, especially in individuals who receive extensive antibiotic treatments to reduce pulmonary exacerbation [5, 6]. It is characterized by reduced microbial diversity, an overgrowth of pathogenic bacteria (*E. coli*, *Clostridium perfringens*), and a depletion of beneficial species (*Lactobacillus*, *Bifidobacterium*). This imbalance exacerbates intestinal inflammation, compromises the intestinal barrier, and may contribute to systemic and pulmonary inflammation through the gut-lung axis [1, 7].

Probiotics, defined as live microorganisms that confer health benefits to the host when consumed in adequately, have demonstrated potential in modulating gut microbiota, enhancing intestinal barrier function, and reducing inflammation. They have been used successfully in conditions such as childhood gastroenteritis, atopic disorders, pouchitis, and inflammatory bowel diseases [8–13]. In cystic fibrosis, gut microbiota is frequently disrupted due to extensive antibiotic use, increased intestinal permeability, and an imbalance of immune mediators. These factors make CF patients particularly suitable candidates for probiotic supplementation [14–18]. *Lactobacillus reuteri* (*L. reuteri*) is a probiotic with anti-inflammatory and immunomodulatory properties that may benefit individuals with cystic fibrosis (CF). It has shown potential in reducing intestinal inflammation, improving gut microbiota balance, and enhancing mucosal barrier function, which are often compromised in CF [19–21]. Furthermore, *L. reuteri* may indirectly support respiratory health by mitigating systemic inflammation and modulating immune responses [22]. *L. reuteri* is sensitive to heat and is not heat-resistant, with temperatures above 40 °C (104 °F) reducing its viability, so warm water below this threshold is preferable [23]. When taken with yogurt, probiotic strains present in the yogurt could compete with *L. reuteri* for adhesion sites and nutrients, potentially influencing its efficacy, though this interaction depends on the specific strains and individual microbiome conditions [23]. Using both together may still provide overall probiotic benefits, but their compatibility should be considered. However, their role in CF remains under investigation, with previous studies yielding mixed results. In pediatrics with CF, extensive antibiotic use, increased intestinal permeability, and imbalances in immune mediators contribute to gut dysbiosis, making probiotic supplementation a promising therapeutic option.

In this study, by using a prospective randomized, double-blind, placebo-controlled design, we aimed to investigate the effects of probiotics, particularly *L. reuteri*, on various health aspects in children diagnosed with CF, including pulmonary function, gastrointestinal symptoms, growth, and overall quality of life. This article is the first trial of its kind in Iran, contributing to the growing body of evidence on the therapeutic potential of probiotics in CF management.

Methods and material

Study design and population

This randomized, double-blind, placebo-controlled clinical trial with parallel groups was retrospectively registered IRCT registration number: IRCT20240105060622N1 (Registration date: 2024-08-16). The study aimed to evaluate the effects of probiotics on children with CF.

The study included 110 patients with cystic fibrosis who attended the CF clinic at Tehran Children's Medical Center in 2024. Participants were recruited after the study protocol received approval from the Ethics Committee of Tehran University of Medical Sciences (Ethics Code: IR.TUMS.CHMC.REC.1402.114).

Inclusion criteria

- Children aged 6 to 12 years diagnosed with CF according to the Cystic Fibrosis Foundation guidelines [24].
- Presence of pancreatic insufficiency with fecal elastase levels below 200 μg/g.

- Written informed consent from parents or guardians.
- Participants were allowed to use dornase alfa, mucolytics, and ivacaftor based on a fixed, defined dose. But, when patients do receive antibiotics, efforts should be made to administer the probiotic within a 4 -h interval in order to minimize interference of the antibiotics with the probiotic.

Exclusion criteria

- Patients with immunodeficiency, type 1 or 2 diabetes, cardiovascular, hepatic, gastrointestinal (celiac, IBD or IBS, cirrhosis), gastrointestinal surgery, and ventilator-dependent respiratory failure.
- Withdrawal from participation at any stage.
- Use of probiotic supplements, prebiotics, synbiotics or any foods or drug fortified with these supplements during the last three months.

Study protocol

Eligible participants were randomized into two groups using a block randomization method. The study was double-blinded; neither the participants nor the statistician analyzing the data were aware of group assignments.

1. Probiotic Group: Received *L. reuteri* (Rutaflor, CFU/d) daily for one month.
2. Placebo Group: Received a placebo (maltodextrin) identical in appearance, taste, smell, and administration method to the probiotic.

The probiotics were provided by the Faradaru Fanavar Mehr Company. Sachets were dissolved in lukewarm water (At temperatures well below 40 °C), yogurt (no content of any probiotics), or food, with dosing based on age: 2–5 years: 1 sachet per day and 5–14 years: 2 sachets per day. Also, the admission rate of patients after the intervention period was calculated using the following formula, and patients whose acceptance rate is less than 80% were excluded from the study.

Acceptance rate = number of packages received at the beginning of the study/number of packages consumed at the end of the study * 100.

Outcome measures

After a one-month intervention with placebo or probiotics, the aforementioned outcomes were assessed at baseline, one month after the intervention, and at a three-month follow-up:

1. Demographic and anthropometric data including age, sex, height, weight, and BMI. Weight was assessed using a Seca portable digital scale manufactured in Germany, which has a precision of 100 g. The measurement was taken with minimum clothing and without wearing shoes. The height was determined using a stadiometer, which has a precision of 0.5 cm, and the measurement was taken without wearing shoes. Body Mass Index (BMI) was computed using the formula: weight (in kilograms) divided by height squared (in meters).
2. The Fecal Fat Test was evaluated using quantitative analysis utilizing light microscopy to count fat cells in a random stool sample.
3. Quality of Life has been assessed using the validated Cystic Fibrosis Quality of Life Questionnaire (CFQ). It includes age-specific versions for children, adolescents, and adults, covering physical, emotional, social, and treatment-related domains. Responses are typically scored on a Likert scale, with higher scores indicating better quality of life. This comprehensive tool aids in evaluating the impact of CF and its treatments on daily living and overall well-being [25].
4. Samples of Throat Cultures were collected from the nasal and posterior pharyngeal areas using swabs, cultured on blood agar or chocolate agar, and analyzed for microbial growth.
5. Spirometry tests, including Forced Expiratory Volume in the First Second (FEV1) and Forced Vital Capacity (FVC) measured to evaluate pulmonary function. The type of spirometer used to perform the functional tests was a pneumotachograph-based spirometer. The recent ATS/ERS standard for interpreting routine lung function tests recommends using Global Lung function Initiative (GLI) reference equations for spirometry and lung volumes [26]. After recording height, weight, and sex, the child is seated on a chair or may stand. There are four steps of the forced vital capacity (FVC) manoeuvre, the most commonly used manoeuvre: (1) Rapid and maximal inspiration with lips tightly around the mouthpiece, (2) A "blast" of expiration, (3) continued blowing of air fast for 6 s in children (although it may be 3 s in younger children) and finally, (4) complete inspiration. The last inspiration step is optional and only required if we need inspiratory parameters. According to the 2019 ATS spirometry update, there is no requirement for a minimum forced expiratory time [27]. A nose clip is recommended while performing spirometry to avoid exhalation through the nose [27]. However, no differences in FEV1 or FVC measurements in children with and without nose clips were noted.

Sample size

The required sample size was calculated based on the mean FEV1% in the probiotic group (74.3 ± 26.3) and

placebo group (68.5 ± 33.8) from a prior study, with a type I error of 5% and power of 80%. Using the formula for comparing two means, a minimum total of 108 participants (54 in each group) was estimated.

Randomization and allocation concealment

Permuted block randomization sequences were created by the randomization website (www.randomization.com). Participants were assigned randomly (1:1 ratio) to either the probiotic or the control groups. The recruitment of participants is shown in Fig. 1.

An independent staff member randomly assigned the participants to one of the two interventions. The treatment allocation was concealed from all researchers using sequentially numbered sealed opaque envelopes. These envelopes were opened sequentially in the presence of participants during their initial visit.

Blinding

Before enrollment, participants were unaware of their group assignments, ensuring blinding. Researchers and laboratory technicians evaluating the outcomes were also blinded to the intervention sequences. To maintain concealment during randomization, unique codes were generated by specialized software and placed on the pharmaceutical packaging. This approach ensured that neither participants nor researchers knew which group received the probiotic or placebo. The supplier of the probiotic and placebo incorporated these codes into the packaging. Each participant received a coded medicine package based on the predetermined random sequence, which was designed to be entirely unpredictable.

Statistical analysis

Data were analyzed using SPSS software. Data of the Qualitative groups were compared between groups using appropriate tests, independent t-test and chi-square tests for parametric data and Mann-Whitney U test for non-parametric, and mean comparison across Quantitative groups was assessed using one-way ANOVA test. All participants who were randomly assigned to the interventions underwent analyses following the intention-to-treat (ITT) principle. Results were considered statistically significant at $P < 0.05$.

Results

Characteristics of the participants

A total of 110 eligible participants with CF were randomly assigned to either probiotic ($n = 55$) or control ($n = 55$) groups. Four participants withdrew from the

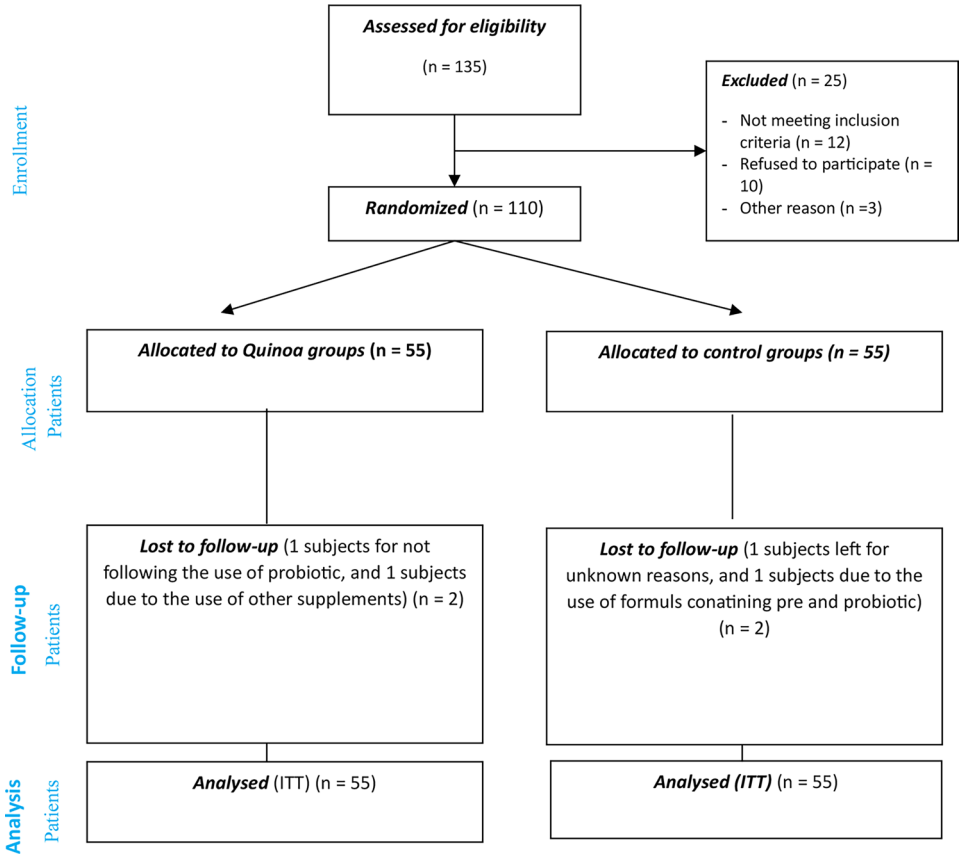

Fig. 1 Consort flow diagram for the trial

Table 1 Comparison of baseline characteristics of the participants

Variable		*Probiotic (n = 55)*	*Placebo (n = 55)*	*P*-value
Age (year)		9.28 ± 1.80	8.76 ± 1.71	0.12
Gender	Male	26 (47.3%)	27 (49.1%)	0.84
	Female	29 (52.7%)	28 (50.9%)	
Weigth (kg)		27.01 ± 8.54	26.26 ± 7.68	0.63
BMI (kg/m$^{2)}$		17.60 ± 3.46	16.57 ± 3.13	0.10
FEV1 (%)		71.52 ± 9.96	69.25 ± 9.85	0.23
Exacerbation (yes), n(%)		13(23.6)	12(21.8)	0.82

Data represented as mean ± SD or n (%)

Independent sample t-test for quantitative variables, chi-square test for categorical variables

study. Finally, all patients (55 in the intervention and 55 in the control groups) entered the analysis with ITT analysis (Fig. 1).

Table 1 presents the baseline characteristics of the study participants. No statistically significant differences were observed between the intervention (probiotic) and control (placebo) groups in terms of age, gender, BMI, FEV1, or the presence of CF exacerbations at baseline.

Table 2 outlines the changes in anthropometric indices (weight and BMI), FEV1, and CFQ scores in the intervention (probiotic) and control (placebo) groups at 4 and 12 weeks:

Weight

Both groups exhibited a statistically significant increase in weight at 12 weeks (P-value < 0.05). At 4 weeks, the control group demonstrated a significantly greater weight increase compared to the intervention group (P-value < 0.05). However, no significant difference in weight change was observed between the two groups at 12 weeks.

BMI and FEV1

No statistically significant differences were observed between the probiotic and placebo groups regarding BMI and FEV1 changes at 4 and 12 weeks. Within the placebo group, BMI significantly decreased at 4 weeks (P-value < 0.05), and FEV1 significantly declined at 12 weeks (P-value < 0.05).Furthermore, FEV1 significantly decreased at 4 weeks in the probiotic group.

CFQ scores

CFQ scores in the probiotic group significantly improved at both 4 and 12 weeks (P-value < 0.05). Moreover, the increase in CFQ scores at 12 weeks was significantly greater in the probiotic group compared to the placebo group (P-value < 0.05).

As illustrated in Table 3 and the corresponding figures (Fig. 1, 2, 3, 4 and 5), no significant differences were observed between the probiotic and placebo groups in the following variables after 12 weeks: Number and percentage of children experiencing exacerbations, Fecal fat excretion, Positive throat cultures, Pulmonary infections, and Pain episodes.

The only statistically significant finding was a reduction in the percentage of panic pain episodes in the probiotic group compared to the placebo group at 4 weeks (P-value = 0.02) (Fig. 6).

Linear Correlation Between CFQ Scores, Age, Weight, and FEV1 have been demonstrated in the Table 4. The findings revealed that there is a significant positive correlation between weight changes and CFQ scores, where each unit increase in weight was associated with an approximately 9-point rise in CFQ scores (P-value = 0.005). However, No significant linear correlation was observed between CFQ scores and the other variables, including age and FEV1

Table 2 Anthropometric indices, FEV1, and CFQ score before and after the intervention in probiotic and placebo groups

Variable		Before	Change from baseline at week 4	Change from baseline at week 12	*P*-value[1]	*P*-value[2]
Weight (Kg)	Probiotic	27.01 ± 8.54	-0.03 ± 0.53	0.33 ± 0.70	0.612	< 0.001
	Placebo	26.26 ± 7.68	0.20 ± 0.43	0.58 ± 0.71	**0.002**	0.002
	P-value[3]	0.63	**0.01**	0.09		
BMI (Kg/m^2)	Probiotic	17.60 ± 3.46	-0.03 ± 0.41	0.05 ± 0.63	0.558	0.580
	Placebo	16.57 ± 3.13	-0.06 ± 0.21	-0.10 ± 0.44	**0.043**	0.126
	P-value[3]	0.10	0.66	0.17		
FEV1(%)	Probiotic	71.52 ± 9.96	-11.25 ± 14.10	-1.79 ± 11.59	**0.018**	0.310
	Placebo	69.25 ± 9.85	-6.04 ± 12.96	-4.85 ± 12.34	0.200	0.010
	P-value[3]	0.23	0.39	0.22		
CFQ Score	Probiotic	227.16 ± 18.75	9.09 ± 19.26	13.17 ± 21.32	**0.002**	< 0.001
	Placebo	225.81 ± 21.38	4.28 ± 18.60	2.72 ± 20.17	0.113	0.375
	P-value[3]	0.73	0.21	**0.02**		

Data repressented as mean ± SD

1: within group comparison at first follow up (Baseline and week 4), paired t-test, 2: within group comparison at first follow up (Baseline and week 12), paired t-test, 3: between group comparison, independent t-test, BMI: Body Mass Index

Table 3 Clinical status and disease severity before and after the intervention in probiotic and placebo groups

Variable		Before	At week 4	At week 12
Exacerbation (yes), n(%)	Probiotic	13(23.6)	11 (20)	10 (18.2)
	Placebo	12(21.8)	7(12.7)	14 (25.5)
	P-value[1]	0.82	0.52	0.63
Fat loss (yes), n(%)	Probiotic	37(67.3)	10 (18.2)	7(12.7)
	Placebo	38(69.1)	25 (45.5)	7(12.7)
	P-value[1]	0.83	0.08	1.00
Throat Culture (Positive), n(%)	Probiotic	25 (45.5)	16 (29.1)	11 (20.0)
	Placebo	25(45.5)	21 (38.2)	14 (25.5)
	P-value[1]	1.00	0.59	0.78
Infection Lung(Positive), n(%)	Probiotic	43(78.2)	15 (27.3)	26(47.3)
	Placebo	44 (80.0)	31 (56.4)	29(52.7)
	P-value[1]	0.81	0.07	0.82
Panic Pain (Positive), n(%)	Probiotic	44 (80.0)	10 (18.2)	17(30.9)
	Placebo	39 (70.9)	23 (41.8)	24(43.6)
	P-value[1]	0.26	**0.02**	0.34

Data represented as n(%)

1: between group comparison, Chi-square

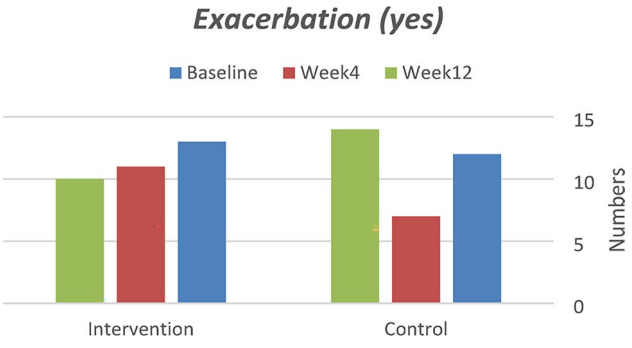

Fig. 2 Pulmonary exacerbations in both groups

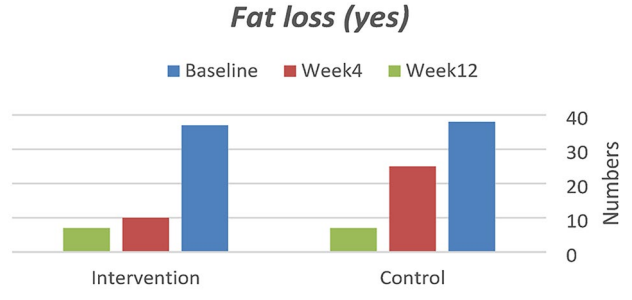

Fig. 3 Fat loss distribution in both groups

Discussion

The present study aimed to evaluate the effects of the *L. reuteri* probiotic on improving respiratory and gastrointestinal symptoms and growth in patients with cystic fibrosis. Our findings showed that weight significantly increased in both intervention and control groups after 12 weeks. However, the two groups had no significant difference in weight gain at the 12-week mark. Similarly,

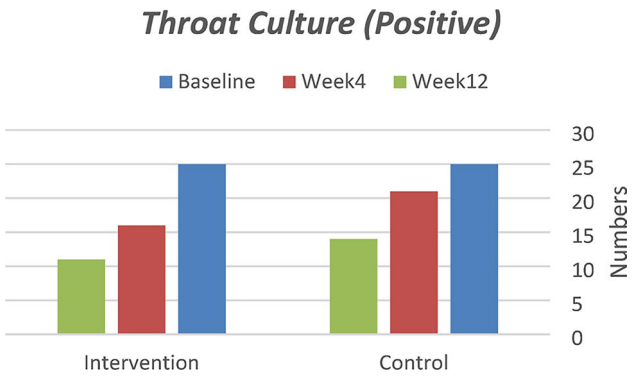

Fig. 4 Throat culture results in both groups

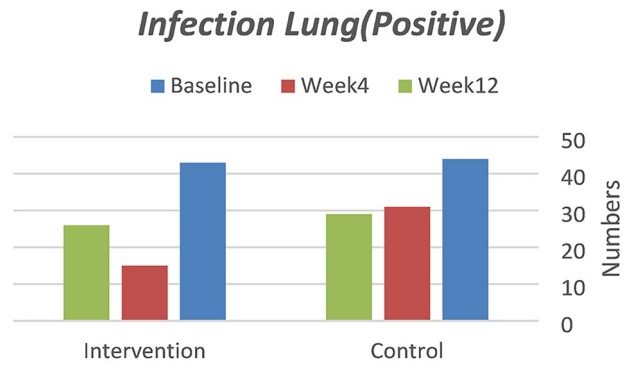

Fig. 5 Pulmonary infections in both groups

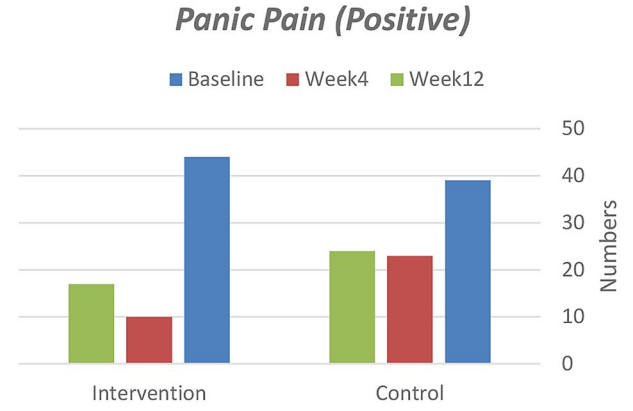

Fig. 6 Panic pain episodes in both groups

Table 4 Relationship between age, FEV1, and weight with CFQ score

	CFQ score change		
	R^2	B coefficient	P-value
Age	0.009	1.093	0.397
Weight change	0.091	9.011	0.005
FEV1 change	0.005	0.129	0.507

*P-value is less than 0.05 and significant

- Multivariate Linear regression analysis has been used

no significant differences were observed between the probiotic and placebo groups regarding changes in BMI or FEV1 at either 4 or 12 weeks. Notably, CFQ questionnaire scores in the intervention group significantly improved at both 4 and 12 weeks, with the increase at 12 weeks being significantly greater in the probiotic group compared to the placebo group. No significant differences were found between the groups in terms of the number and percentage of children experiencing exacerbations, fecal fat excretion, positive throat cultures, pulmonary infections, or pain episodes at 12 weeks. The only significant finding was a reduction in pain episodes in the probiotic group compared to the placebo group after 4 weeks of intervention.

Numerous studies have investigated the potential effects of oral probiotics on reducing intestinal inflammation and improving respiratory symptoms in CF patients. However, the findings from these clinical trials remain inconsistent, making it difficult to draw definitive conclusions about the efficacy of probiotics in mitigating CF manifestations [19, 28].

Furthermore, several studies have evaluated the efficacy of probiotics on growth, gastrointestinal symptoms, and respiratory outcomes in CF patients. In a study by Weiss et al., the impact of probiotics on pulmonary symptoms in CF patients was assessed. The findings revealed a significant reduction in pulmonary exacerbations six months after probiotic supplementation. However, after probiotic treatment, no notable changes were observed in pulmonary function tests (PFTs), sputum cultures, neutrophil counts, or IL-8 levels. These results regarding pulmonary exacerbations differ from our findings. This discrepancy could be attributed to variations in sample size, probiotic supplementation duration, or the type and dosage of probiotics used. In the study by Weiss et al., the probiotics administered included *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus* at a dosage of 6×10^9 CFU/d, whereas our study exclusively used *Lactobacillus reuteri*. It is also noteworthy that the reduction in pulmonary exacerbations observed in the Weiss et al. study was significant only in patients treated with oral antibiotics as outpatients and not in those receiving intravenous antibiotics as inpatients [21]. Bruzzese et al. treated 19 children with CF using *Lactobacillus GG* at a dosage of 6×10^9 CFU/day for six months in this prospective crossover study. The results were compared with a placebo group. The findings demonstrated a significant reduction in pulmonary exacerbations and hospitalizations, along with improvements in FEV1 and BMI [29]. These results contrast with our findings. This discrepancy could potentially be explained by differences in sample size and the longer duration of probiotic supplementation in the study by Bruzzese et al.

Evaluating quality of life (QoL) in chronic diseases such as cystic fibrosis is increasingly recognized as an essential adjunct to clinical outcome parameters in assessing disease progression. Improved lung function directly enhances nutritional status, leading to better QoL [29]. Various pulmonary rehabilitation programs and nutritional supplements have been proposed to improve lung function and QoL in CF patients [30]. Previous studies assessing the effects of probiotics on the QoL of CF patients remain relatively limited. This study demonstrated a significant improvement in QoL among patients receiving probiotics compared to those in the placebo group three months after completing probiotic therapy. These findings suggest that probiotic supplementation may temporarily affect QoL, and continuous use may be necessary to maintain long-term benefits. In a study by Jafari et al., 20 patients in the probiotic group were treated for one month with a probiotic combination including *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium infantis*, and *Lactobacillus bulgaricus* at a dosage of 2×10^9 CFU/d. Meanwhile, 17 patients in the control group received placebo capsules. The results showed a significant improvement in the mean total quality of life (QoL) score in the probiotic group compared to the placebo group at three months. However, this improvement was no longer significant at six months of probiotic treatment. Additionally, pulmonary exacerbations significantly decreased in the probiotic group [31]. Our findings regarding improved QoL scores three months after probiotic consumption align with those of Jafari et al. A more reliable judgment about the relationship between probiotic therapy and QoL in CF patients may require longer treatment durations and extended follow-up periods.

In the study by Biervliet et al., 25 CF patients were treated with a probiotic combination containing *Lactobacillus rhamnosus* SP1 (DSM 21690) and *Bifidobacterium animalis* spp. BLC1 (LGM23512) at a dosage of 10^{10} CFU. The results showed no significant changes in clinical parameters, including BMI, FEV1, abdominal pain, or pulmonary exacerbations. Additionally, fecal calprotectin (FCP) concentrations did not change significantly in those receiving probiotics [20]. The findings of this study align with the results of the current research. In a study by Dinardo et al., CF patients treated with the probiotic *Lactobacillus reuteri* ATCC55730 showed a significant reduction in pulmonary exacerbations and the number of upper respiratory tract infections (URTIs) compared to the placebo group. However, no significant differences were observed in the bacterial composition of sputum cultures [32]. The findings regarding the lack of impact of probiotics on sputum cultures are consistent with the results of our study. In contrast to our findings,

a recent Cochrane review of 14 randomized, controlled trials showed that probiotics were superior to placebo in reducing the incidence of upper respiratory tract infections (URTIs) and, consequently, the need for antibiotics [33]. Additionally, another study demonstrated that feeding infants with formula containing *Lactobacillus* significantly reduced the risk of URTIs [22].

In line with our findings on the lack of efficacy of probiotics in improving FEV1, several studies have suggested that the failure to improve FEV1 may be linked to the chronicity of pulmonary disease, leading to irreversible damage. It has been proposed that inflammatory markers in induced sputum might be more sensitive than pulmonary function tests in assessing treatment effectiveness and in reflecting the underlying mechanisms of inflammation and infection [34, 35]. In the review of two clinical trials involving 91 participants, Coffey et al. reported that probiotics did not affect height, weight, or BMI. However, they observed a reduction in gut dysbiosis among the participants in their study [28]. The beneficial effects of probiotics are thought to stem from their ability to modulate the gut microbiota and mitigate the harmful impact of inflammatory cytokines (TNF-α and IFN-γ) on epithelial function, which helps maintain the integrity of the intestinal barrier [36].

Recent studies suggest that probiotics may offer benefits for individuals with cystic fibrosis (CF) by reducing intestinal inflammation and the frequency of pulmonary exacerbations [37–39]. However, the evidence remains limited due to variability in study designs and the quality of data, making it difficult to identify optimal strains, dosages, and treatment durations for routine clinical use. Additionally, probiotics appear to influence gut colonization by pathogenic bacteria positively, support the structural integrity of the intestinal mucosal barrier, regulate the production of beneficial metabolites, modulate immune activity, and stimulate vitamin synthesis [37–39]. The effects, however, can vary based on the probiotic type, dosage, duration of administration, and individual conditions.

Probiotics are administered orally, and their mechanism of action involves modulating the gut microbiota, influencing the host immune response, and enhancing the intestinal barrier. There is increasing evidence that probiotic species may play a role in treating inflammatory bowel disease and other gastrointestinal disorders associated with alterations in the gut microbiota. It has been shown that intestinal inflammation is a key feature of cystic fibrosis (CF). Studies indicate that probiotics can reverse epithelial damage caused by cytokines, reducing intestinal inflammation in CF patients. Suppressing the intestinal inflammatory response may help maintain the integrity of the gut barrier, reduce bacterial and environmental trigger translocation, and lower pulmonary inflammation. Such modulation could be achieved through probiotic therapy [40]. Probiotics may reduce pain in patients with cystic fibrosis (CF) through several mechanisms. They help restore gut microbiota balance, reducing pro-inflammatory cytokines like TNF-α and IL-6, which are associated with pain [20]. Probiotics also improve gut barrier integrity, preventing systemic inflammation caused by microbial translocation [36]. Furthermore, they modulate the gut-brain axis via the vagus nerve and neuroactive compounds, reducing pain perception. Short-chain fatty acids (SCFAs) produced by probiotics, such as butyrate, exhibit anti-inflammatory properties that can alleviate gastrointestinal pain commonly experienced by CF patients [15].

This study also has several strengths. It is the first study in Iran to evaluate the effects of probiotics on improving respiratory symptoms, gastrointestinal symptoms, growth, and quality of life in children with cystic fibrosis through a randomized controlled trial with a placebo group. However, there are several limitations to this study. First, while we conducted this study as a prospective, randomized, and controlled trial, the fact that it was conducted at a single center limits the generalizability of our results due to patient population and staff characteristics. Second, the study's small sample size is another area for improvement.

Conclusion

In conclusion, probiotic treatment improved the quality of life in patients with cystic fibrosis. However, it did not significantly affect weight, BMI, FEV1, pulmonary exacerbations, fecal fat excretion, throat cultures, pulmonary infections, or pain episodes. The effects of probiotics are temporary, and continuous use may provide more sustained improvements in quality of life. To better evaluate the potential benefits of probiotics in alleviating gastrointestinal and pulmonary symptoms and improving quality of life in CF patients, future prospective, placebo-controlled studies with larger patient populations and more prolonged treatment and follow-up durations are recommended.

Abbreviations

CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Trans-membrane Regulator
L. reuteri	Lactobacillus reuteri
FEV1	Forced Expiratory Volume in the First Second
FVC	Forced Vital Capacity
GLI	Global Lung function Initiative
PFTs	Pulmonary Function Tests
FCP	Fecal Calprotectin
URTIs	Upper Respiratory Tract Infections

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05789-0.

Supplementary Material 1

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Author contributions
P.R, MH.S, M.A: conception, design, statistical analysis, data collection, writing-original draft, supervision.P.R, FM, AK, KE, MR.M: data collection and writing-original draft.All authors approved the final version of the manuscript.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki and its later amendments. This study was approved by the research council and Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran. Written informed consents were obtained from all study participants' parents or other legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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