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Washed microbiota transplantation effectively improves nutritional status in gastrointestinal disease–related malnourished children

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ABSTRACT

Background and aim: Gut microbiota dysbiosis plays a critical role in malnutrition caused by food intolerance and intestinal inflammation in children, which needs to be addressed. We assessed the efficacy and safety of washed microbiota transplantation (WMT) for gastrointestinal disease–related malnourished children.
Methods: This was a prospective observational study involving gastrointestinal disease–related malnourished pediatric patients who underwent WMT. The primary outcome was the clinical response rate at 3 mo post-WMT. Clinical response was defined as an improvement in the children's nutritional status of one level or more. The secondary outcomes were changes in gastrointestinal symptoms, laboratory nutritional indicators, and adverse events during the WMT procedure.
Results: 29 patients undergoing 74 WMTs were included for analysis. In total, 48.3% (14/29) of patients achieved clinical response post-WMT. Gastrointestinal symptoms, including diarrhea, mucous stool, abdominal pain, abdominal distention, and hematochezia, were significantly relieved post-WMT (all $P < 0.05$). Serum albumin and prealbumin levels were increased significantly post-WMT ($P = 0.028$ and 0.028, respectively). Eight self-limiting and transient adverse events, including diarrhea, abdominal pain, and abdominal distension, occurred after WMT.
Conclusion: This study indicated that WMT might be effective and safe for improving nutritional status and gastrointestinal symptoms in gastrointestinal disease–related malnourished children at 3-mo follow-up. WMT was expected to be a new therapeutic option for these patients.

Introduction

Child malnutrition is a major global public health problem [1]. Forty-five percent of child deaths are related to malnutrition. Gastrointestinal disorders, such as inflammatory bowel disease (IBD) and food intolerance, are common causes of malnutrition [2]. These disorders lead to malnutrition through various mechanisms such as malabsorption, chronic gut inflammation, and excessive excretion. Malnutrition can further worsen intestinal damage, resulting in a vicious circle. Therefore, timely treatment of children with gastrointestinal disorders is crucial to preventing malnutrition.

Increasing evidence indicates that childhood malnutrition is linked to gut microbiota [3]. Nutritional support alone may not completely recover the malnutrition phenotype for patients with gastrointestinal disorders [4]. The gut microbiota of children typically matures alongside their growth [5], but in malnourished children, it remains immature compared with their well-nourished counterparts [6]. The potential pathogenic genera, such as *Escherichia* and *Shigella*, are significantly increased in malnourished children, while the level of *Prevotella copri* is lower [7]. Malnutrition phenotypes in children can be transferred to mice by fecal microbiota transplantation (FMT) [4]. Chen et al. found that malnutrition can be alleviated in malnourished children by targeting the manipulation of their gut microbiota through supplementary microbiota-directed food [8], suggesting that gut microbiota is a potential therapeutic target for malnutrition. Recently, Browne et al. emphasized that boosting microbiome science worldwide could save millions of children by starting with gut microbes to treat malnutrition [9].

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FMT is an effective method for gut microbiota dysbiosis-related diseases, such as *Clostridioides difficile* infection (CDI) [10] and IBD [11]. In pediatric patients, FMT has also been reported to be safe and has a positive role in treating CDI, IBD, autism spectrum disorder, and others [12]. Washed microbiota transplantation (WMT) is the new generation of FMT, based on the automatic washing process and related delivery considerations, significantly decreasing FMT-related adverse events (AEs) [13,14]. However, the potential role of WMT in gastrointestinal disease–related malnourishment in children remains unknown. This study was designed to evaluate the efficacy and safety of WMT in improving the nutritional status of children with malnutrition related to gastrointestinal diseases. Additionally, it included assessment of the impact of WMT on gastrointestinal symptoms and laboratory nutritional indicators.

Methods

Study design

This prospective, observational, and single-center study was carried out in the Second Affiliated Hospital of Nanjing Medical University from June 2019 to April 2023, followed the principles of the Declaration of Helsinki, and was reviewed by the Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University. Written informed consent was obtained from the children and/or the children's legal guardians. The inclusion criteria were: (1) body mass index *Z*-score (BMIZ) < -1 and complicated with gastrointestinal disorder, (2) aged 2 to 18 y, (3) underwent WMT treatment, and (4) signed informed consent. The exclusion criteria for this study were: (1) thyroid hormone or growth hormone deficiency, (2) presence of picky and partial eating behaviors, (3) switched therapy during the study, or (4) the follow-up less than 3 mo.

Data collection

Weight and height were measured at baseline and 3 mo post-WMT. This study used age- and sex-specific *Z*-scores for height and body mass index (BMI) to assess the nutritional status of children, calculated according to World Health Organization (WHO) child growth standards [15].

According to the definition from the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition [16], BMIZ < -1 was classified as malnutrition. Subsequently, mild malnutrition was defined as $-2 \leq$ BMIZ < -1, moderate malnutrition as $-3 \leq$ BMIZ < -2, and severe malnutrition as BMIZ < -3. We refer to the moderate malnutrition group and severe malnutrition combination as the moderate-to-severe malnutrition group. Stunting was defined as the height-for-age *Z*-score (HAZ) < -2.

A nutritionist assessed the patients' nutritional status at baseline and the observation endpoint using the Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP) score. The STAMP screens children for nutritional risk in three dimensions: disease risk, dietary investigation, and growth and developmental status. A total score of 1 or less is considered low nutritional risk; a score of 2 to 3 is regarded as intermediate nutritional risk; and a score of 4 or more suggests high nutritional risk [17].

A gastroenterologist recorded patients' gastrointestinal symptoms, including diarrhea, abdominal pain, abdominal distension, mucous stools, and hematochezia at baseline, 1, and 3 mo post-WMT. Abdominal pain and distension were scored from 0 to 10, with higher scores indicating more severe symptoms. Mucous and bloody stools were scored from 0 to 3 (0 = none, 1 = present less than half the time, 2 = present most of the time, and 3 = present continuously).

Laboratory nutritional indicators, including albumin (g/L), prealbumin (mg/dL), and hemoglobin (g/L), were recorded in all children at the baseline and endpoint of observation.

WMT procedure

WMT comprised repeated microfiltration, centrifugation, washing, discarding, and resuspension using an automatic microfiltration machine (GenFMTer, Nanjing, China) in a biosafety level-3 laboratory [14], which has higher safety compared with traditional manual FMT [13]. The purified washed microbiota suspension obtained was delivered to the patients' intestines within 1 h through a mid-gut or colonic transendoscopic enteral tube (TET; diameter 2.7 mm, FMT Medical, Nanjing, China) [18].

Primary and secondary outcomes

The primary outcome of this study was the clinical response rate within 3 mo post-WMT. Patients were considered to have a clinical response if their nutritional status level improved (status of severely malnourished children improved to moderately malnourished or better; status of moderately malnourished children improved to mild malnourished or better; and status of mild malnourished children improved to well-nourished).

The secondary outcomes were changes in HAZ, BMI, STAMP scores, gastrointestinal symptoms, and laboratory nutritional indicators. WMT-related AEs during the WMT procedure were also recorded in detail as a secondary outcome.

We also assessed the additional benefit in malnourished children with IBD. For children with ulcerative colitis (UC), the Pediatric Ulcerative Colitis Activity Index (PUCAI) was used to evaluate the condition. PUCAI scores range from 0 to 85 and are categorized as remission (<10), mild (10-29), moderate (30–64), and severe (65–85) [19]. Clinical response of UC is defined as a decrease in the PUCAI score of more than 20 points from baseline to 3 mo post-WMT. PUCAI scores < 10 lasting for 3 mo was defined as maintenance of remission. For children with Crohn's disease (CD), the Pediatric Crohn's Disease Activity Index (PCDAI) was used to evaluate the condition. PCDAI scores range from 0 to 100 and are categorized as remission (<10), mild (10–27.5), moderate (30–37.5), and severe (40–100) [20]. Clinical response of CD is defined as a decrease in the PCDAI score of more than 12.5 points from baseline to 3 mo post-WMT [21]. PCDAI scores < 10 lasting for 3 mo was defined as maintenance of remission.

Statistical analysis

All statistical processing was performed using IBM SPSS Statistics 26.0 and GraphPad 9.0. For patients' baseline characteristics, means and standard deviations (SDs) are used to describe normally distributed continuous variables, medians and interquartile ranges (IQRs) are used to describe skewed continuity variables, and proportions are used to describe categorical variables. For categorical variables, group comparisons were made using Fisher's exact test. For continuous variables, paired-samples *t*-tests were used for normally distributed variables and Wilcoxon signed-rank tests and Mann-Whitney U test were used for skewed variables. A two-tailed *P*-value < 0.05 was considered statistically significant.

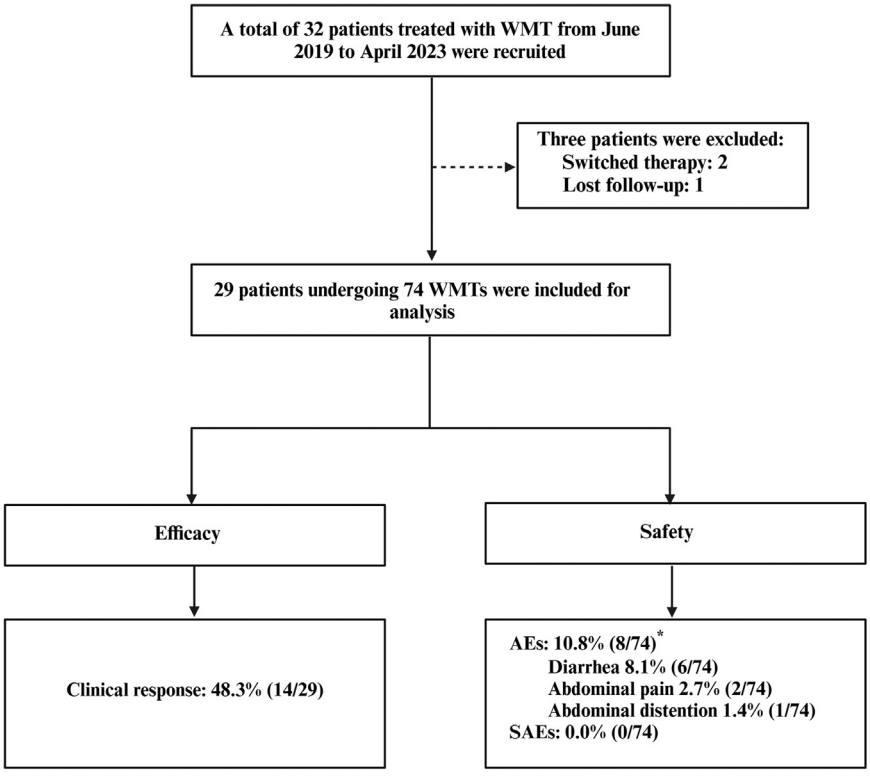

Fig. 1. Study flowchart. *One patient had both abdominal pain and diarrhea. AEs, adverse events; SAEs, severe adverse events; WMT, washed microbiota transplantation.

Results

WMT procedure and baseline characteristics

Thirty-two patients from June 2019 to April 2023 were recruited into the study, and three patients were excluded due to switching therapy or loss to follow-up. Finally, 29 patients were included for analysis, as shown in Fig. 1. Among the participants, 37.9% (11/29) were diagnosed with IBD, 34.5% (10/29) were diagnosed with food intolerance (FI), and 13.8% (4/29) had a history of gastrointestinal surgery (Table 1). Of the four pediatric patients with a history of gastrointestinal surgery, one underwent rectal resection for congenital megacolon, one underwent partial small bowel resection for cryptogenic multifocal ulcerous stenosing enteritis, one underwent partial small bowel resection for intestinal obstruction, and one underwent ileostomy for intestinal perforation. The median age was 11.0 y old, mean BMI was 13.7 kg/m^2, mean BMIZ was −2.5, mean HAZ was −0.4, and median STAMP score was 6.0. Among 29 patients, 31.0% (9/29) were in the mild malnutrition group, 41.4% (12/29) were in the moderate malnutrition group, and 27.6% (8/29) were in the severe malnutrition group. Appropriately, 31.0% (9/29) of children underwent WMT through mid-gut TET and 69.0% (20/29) through colonic TET (Table 1).

Incidence rate of gastrointestinal symptoms in children with mild versus moderate-to-severe malnourishment

Compared with the mild malnutrition group, the moderate-to-severe malnutrition group had a significantly higher incidence rate of diarrhea (P = 0.005). The incidence rates of other gastrointestinal symptoms trended higher in the moderate-to-severe malnourished group compared with the mild malnourished group, although there was no statistically significant difference (Table 2).

Efficacy of WMT on nutritional status

As illustrated in Fig. 2, compared with baseline, the BMIZ, BMI, and STAMP scores significantly improved 3 mo post-WMT (P = 0.001, < 0.001, and 0.002, respectively). A total of 48.3% (14/

Table 1
Characteristics of patients at baseline

Characteristics	Results (n = 29)
Age, y, median (IQR)	11.0 (7.4–14.8)
Sex, male, n (%)	17 (58.6)
Disease duration, mo, median (IQR)	20.0 (6.5–48.0)
Disease type, n (%)	
Inflammatory bowel disease	11 (37.9)
Food intolerance	10 (34.5)
Other diseases*	8 (27.6)
History of gastrointestinal surgery, n (%)	4 (13.8)
BMIZ, mean ± SD	−2.5 ± 1.0
−2 < BMIZ < −1, n (%)	9 (31.0)
−3 < BMIZ < −2, n (%)	12 (41.4)
BMIZ < −3, n (%)	8 (27.6)
BMI, kg/m^2, mean ± SD	13.7 ± 1.5
HAZ, mean ± SD	−0.4 ± 1.6
STAMP score, median (IQR)	6.0 (5.0–7.5)
Delivery route of WMT, n (%)	
Mid-gut TET	9 (31.0)
Colonic TET	20 (69.0)
Frequency of WMT, median (IQR)	3 (2–3)

BMI, body mass index; BMIZ, body mass index Z-score; HAZ, height-for-age Z-score; IQR, interquartile range; SD, standard deviation; STAMP, Screening Tool for the Assessment of Malnutrition in Pediatrics; TET, transendoscopic enteral tube; WMT, washed microbiota transplantation

* The other diseases included *Clostridioides difficile* infection (n = 1), chronic pseudointestinal obstruction (n = 1), Hirschsprung disease (n = 1), superior mesenteric artery syndrome (n = 1), gut graft-versus-host disease (n = 2), celiac disease (n = 1), and cryptogenic multifocal ulcerous stenosing enteritis (n = 1).

Table 2
Incidence rate of gastrointestinal symptoms in children with mild versus moderate-to-severe malnourishment

	Mild malnutrition group (n = 9)	Moderate-to-severe malnutrition group (n = 20)	*P*-value
Diarrhea	1/9 (11.1%)	14/20 (70.0%)	0.005*
Mucous stool	2/8 (25.0%)	12/19 (63.2%)	0.103
Abdominal pain	2/9 (22.2%)	10/20 (50.0%)	0.234
Abdominal distention	2/7 (28.6%)	7/18 (38.9%)	1.000
Hematochezia	0/8 (0.0%)	7/19 (36.8%)	0.068

Fisher exact test.
*$P < 0.05$.

29) of patients achieved a clinical response 3 mo post-WMT (Fig. 1). As shown in Fig. 2D, we evaluated the change in children's nutritional status based on BMIZ before and 3 mo post-WMT. Post-WMT, in the severe malnutrition group, 25.0% (2/8) of children were evaluated as having moderate malnutrition and 25.0% (2/8) had mild malnutrition. In the moderate malnutrition group, 41.7% (5/12) of children improved to mild malnutrition, and 16.7% (2/12) to the well-nourished group, post-WMT. In the mild malnutrition group, 33.3% (3/9) were evaluated as well-nourished post-WMT. There was no significant difference in HAZ before and after WMT treatment (Fig. 2E).

A total of 31.0% (9/29) underwent 3 mo of exclusive enteral nutrition (EEN) after WMT; the remainder were on the same diet as baseline. We divided patients into two subgroups based on whether they underwent EEN. The median BMIZ of the WMT with EEN subgroup trended lower compared with that in the WMT subgroup (Supplementary Fig. 1, −2.77 versus −2.29, $P = 0.062$). The serum levels of albumin in the WMT with EEN subgroup were significantly lower than those in the WMT subgroup (Supplementary Fig. 1, 37.2 versus 45.3, $P = 0.043$). BMIZ was significantly improved in those who did not undergo EEN, as shown in Supplementary Fig. 1.

In the etiology of FI, 50.0% (5/10) of malnourished children achieved clinical response 3 mo post-WMT, and the mean BMIZ significantly improved from −2.31 to −1.68 at 3 mo post-WMT compared with baseline (Supplementary Fig. 3, $P = 0.047$).

Efficacy of WMT for gastrointestinal symptoms

As shown in Fig. 3A, diarrhea (51.7%) was the most common gastrointestinal symptom, followed by mucous stool (48.3%), abdominal pain (37.9%), abdominal distention (31.0%), and hematochezia (24.1%). Diarrhea was significantly relieved at 1 and 3 mo post-WMT (Fig. 3B, $P = 0.019$ and 0.016, respectively). Scores for mucous stool, abdominal pain, and hematochezia significantly decreased at 1 and 3 mo post-WMT (Fig. 3C, D, and F). Abdominal distention was significantly lower at 3 mo post-WMT than at baseline (Fig. 3E, $P = 0.011$).

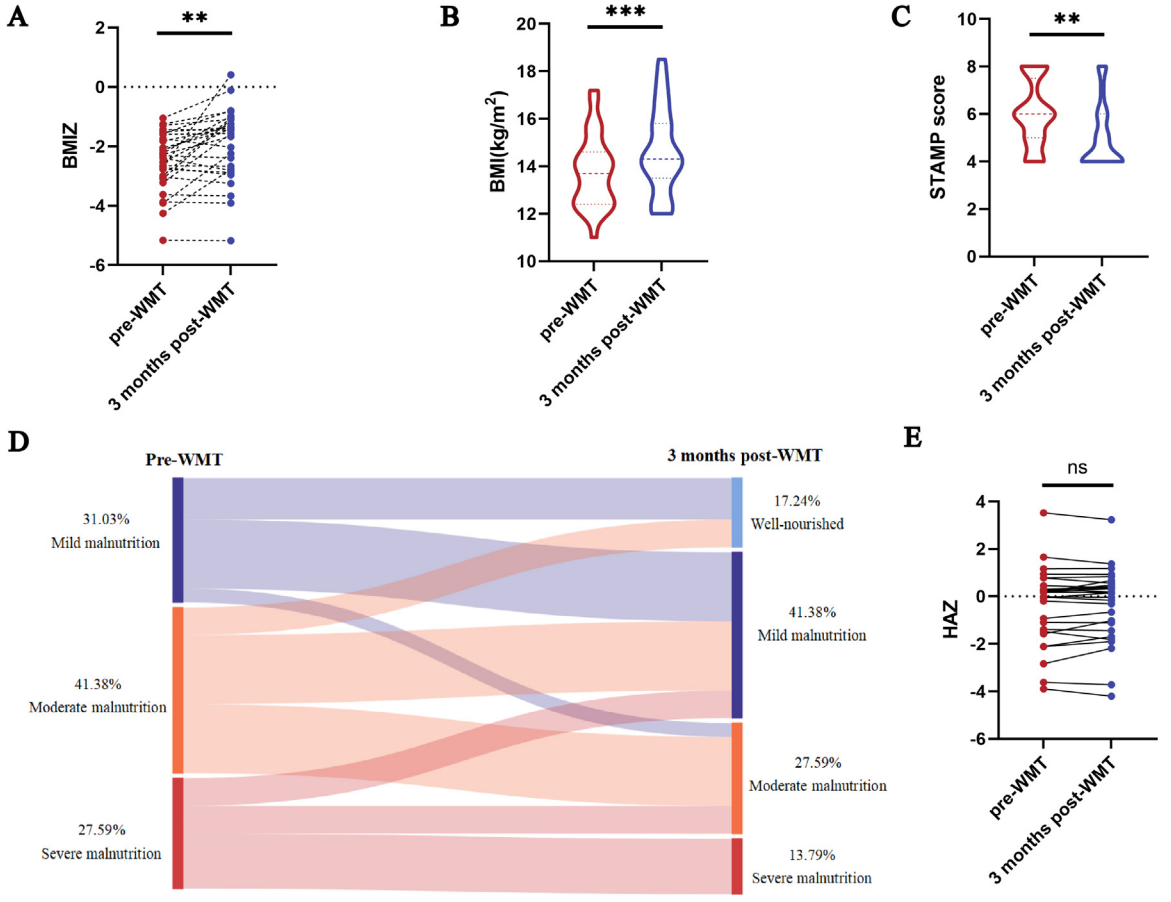

Fig. 2. Efficacy of WMT for nutritional status in children. (A) BMIZ of children before and 3 mo post-WMT was analyzed by paired-samples *t*-tests. (B) BMI before and 3 mo post-WMT was analyzed by paired-samples *t*-tests. (C) STAMP scores before and 3 mo post-WMT was analyzed using Wilcoxon signed-rank tests. (D) Children's nutritional status change based on BMIZ before and 3 mo post-WMT. (E) HAZ of children before and 3 mo post-WMT analyzed by Wilcoxon signed-rank tests. **$P < 0.01$, ***$P < 0.001$. BMI, body mass index; BMIZ, body mass index Z-score; HAZ, height-for-age Z-score; WMT, washed microbiota transplantation.

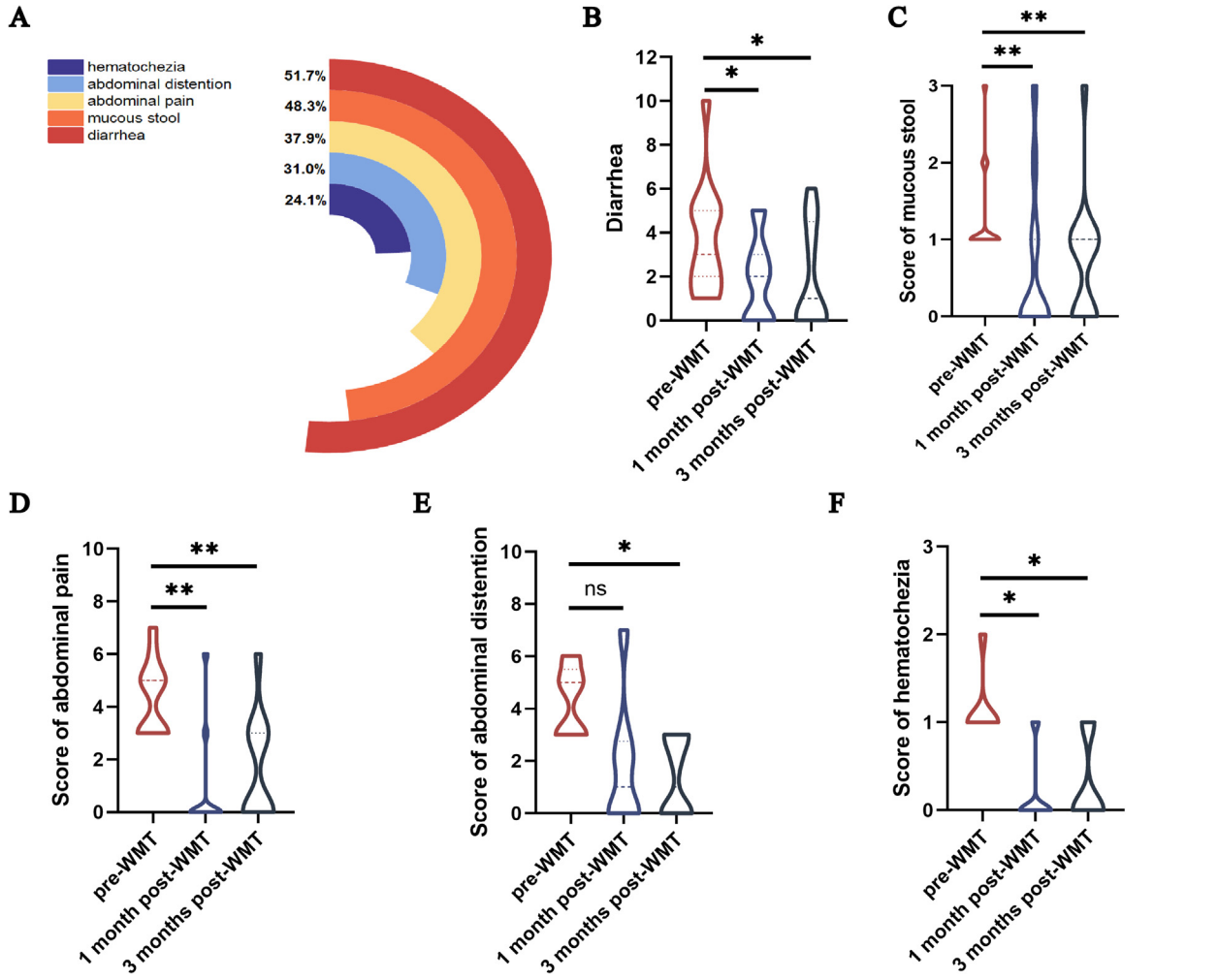

Fig. 3. Incidence of gastrointestinal symptoms in children and efficacy of WMT. (A) Occurrence rate of complicated gastrointestinal symptoms in children. Changes in frequency and/or scores for gastrointestinal symptoms before and after WMT, including (B) diarrhea (n = 15), (C) mucous stool (n = 14), (D) abdominal pain (n = 11), (E) abdominal distention (n = 9), and (F) hematochezia (n = 7), all of which were calculated by Wilcoxon signed-rank tests. * $P < 0.05$, ** $P < 0.01$. WMT, washed microbiota transplantation.

Changes in laboratory nutritional indicators post-WMT

We evaluated the changes in patients' abnormal baseline laboratory nutritional indicators post-WMT, and 6 had below-normal albumin (typical range: 40.0–55.0 g/L), 13 had low prealbumin (typical range: 20.0–40.0 mg/dL), and 4 had low hemoglobin (typical range: 110.0–149.0 g/L for 6–59 mo, 115.0–149.0 g/L for 5–11 y, and 120.0–149.0 g/L for 12 y and older). Both albumin and prealbumin levels were significantly improved post-WMT (P = 0.028 and 0.028, respectively). Fig. 4C shows that the median serum hemoglobin levels increased from 91 g/L to 114 g/L post-WMT, although there was no statistically significant difference (P = 0.066), as shown in Fig. 4C.

Additionally, we compared the changes in laboratory nutritional indicators across different causes of IBD and FI. At baseline, children with IBD showed abnormal laboratory nutritional indicators, specifically albumin and prealbumin levels. In our study, three subjects had albumin levels below the normal range, and four subjects exhibited low prealbumin levels. Both serum albumin and prealbumin levels showed an increasing trend from baseline, with the median serum albumin level increasing from 38.4 g/L to 44.3 g/L (Supplementary Fig. 2, P = 0.109) and median serum prealbumin level increasing from 15.2 mg/dL to 17.2 mg/dL (Supplementary Fig. 2, P = 0.068). The abnormalities in laboratory nutritional indicators in children with FI were centered on prealbumin, which was below normal in six individuals at baseline. Although not statistically different, the mean serum prealbumin exhibited an upward trend from 17.2 mg/dL to 19.2 mg/dL 3 mo post-WMT (Supplementary Fig. 3, P = 0.345).

Safety of WMT

The incidence rate of WMT-related AEs was 10.8% (8/74), with diarrhea in 8.1%, abdominal pain in 2.7%, and abdominal distension in 1.4% of patients (one patient had both abdominal pain and diarrhea). All these AEs were self-limiting symptoms without intervention, and no severe AEs occurred during observation. The incidence rate of AEs was 9.5% (2/21) in the mild malnutrition group and 10.9% (6/55) in the moderate-to-severe malnutrition group, with no significant difference between the groups (P = 1.000). We compared the incidence rate of WMT-related AEs between two kinds of delivery routes. There was no significant difference between the two groups (mid-gut TET versus colonic TET, 15.0% versus 9.3%, P = 0.674). We further compared the incidence rate of AEs between

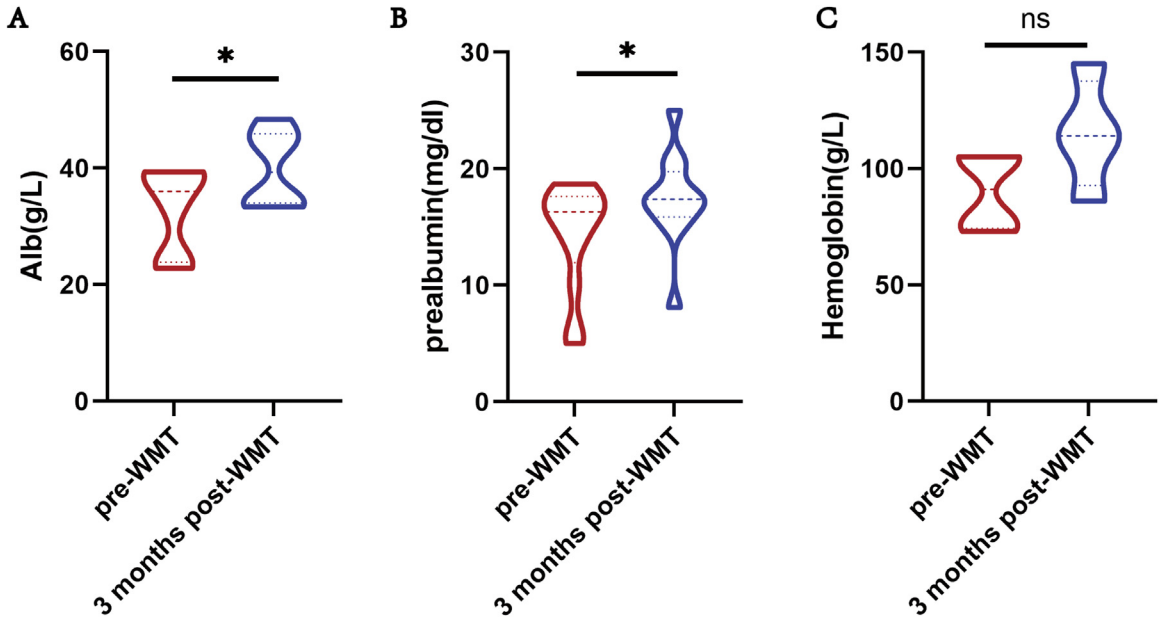

Fig. 4. The effect of WMT on laboratory nutritional indicators. Changes in laboratory nutritional indicators 3 months post-WMT, including albumin (A, n = 6), prealbumin (B, n = 13), and hemoglobin (C, n = 4). Prealbumin was calculated using paired-sample *t*-tests, and the others were calculated using Wilcoxon signed-rank tests. Alb, albumin; WMT, washed microbiota transplantation.

different diseases, with a relatively high incidence of AEs in children with FI compared with children with other diseases, but there was no statistical difference (FI versus other diseases, 17.2% versus 6.7%, $P = 0.250$). In children with IBD, the incidence of AEs was 4.3% (1/23).

Additional benefit in malnourished children with IBD

We additionally recorded the disease characteristics and medication history in the IBD cohort among the malnourished children, as shown in Table 3. Of these children with IBD, 36.4% (4/11) were in remission at baseline, and 75% (3/4) maintained remission 3 mo post-WMT. Four children underwent EEN; three had CD, and one had UC. The clinical response rate of IBD was 57.1% (4/7). The rate of clinical response of malnutrition status in the IBD cohort was 45.5% (5/11), comparable to the rate of clinical response of malnutrition status in the entire cohort (Table 3). The mean BMIZ improved from −2.16 to −1.60 in subjects with IBD at 3 mo post-WMT compared with baseline, although there was no statistical significance (Supplementary Fig. 2, $P = 0.091$).

Discussion

In this observational study, WMT had a positive impact on the nutritional status of children suffering from gastrointestinal disease–related malnutrition. Additionally, it was observed that WMT relieved gastrointestinal symptoms in these patients.

Mild malnutrition is usually associated with acute events such as illnesses, while moderate-to-severe malnutrition is associated with the accumulation of chronic undernutrition [16]. Gastrointestinal disorders are particularly prone to the progression from mild to moderate-to-severe malnutrition. Many gastrointestinal diseases, such as food allergy, IBD, and CDI, are frequently accompanied by a high prevalence of moderate-to-severe malnutrition. In a multicenter observational study, the prevalence of moderate-to-severe malnutrition in IBD was 16% [22]. A retrospective cohort study revealed that children with food allergies experienced significant growth impairment compared with those without food allergies [23]. Our findings indicate that moderately-to-severely malnourished children had a high incidence rate of gastrointestinal symptoms, especially diarrhea, which aligns with previous research [24]. Nearly 13.5% of cases of growth retardation are attributed to diarrhea [1], one of the most common causes of child malnutrition. This condition increases the healthcare burden, lengthens hospitalization, and raises mortality rates among malnourished children [25]. Treating gastrointestinal symptoms in malnourished children is essential to breaking the vicious cycle of

Table 3
Basic characteristics and clinical responses of malnourished children with IBD who underwent WMT treatment

Characteristics	Total (N = 11)
Male, n (%)	6 (54.5)
Age, y, mean ± SD	12.6 ± 3.0
Duration of disease, mo, median (IQR)	12 (12–36)
Paris Classification of extent of UC (n = 5), n (%)	
E3	5 (100)
Paris Classification of CD except growth (n = 6), n (%)	
A1abL1B1	1 (16.7)
A1aL2B1p	1 (16.7)
A1aL3B1	1 (16.7)
A1bL1B1	1 (16.7)
A1bL3B3p	1 (16.7)
A1bL3B2+3p	1 (16.7)
Clinical activity of disease at baseline, n (%)	
Remission	4 (36.4)
Mild	3 (27.3)
Moderate	3 (27.3)
Severe	1 (9.1)
Concomitant treatment, n (%)	
5-ASA	4 (36.4)
Immunosuppressants	1 (9.1)
Biologics	2 (18.2)
EEN	4 (36.4)
Clinical response of malnutrition, n (%)	5 (45.5)
Clinical response of IBD (n = 7)*, n (%)	4 (57.1)
Maintenance of clinical remission of IBD (n = 4), n (%)	3 (75)

IQR, interquartile range; SD, standard deviation; UC, ulcerative colitis
*Seven patients in the active phase at baseline were evaluated.

gastrointestinal disorders and malnutrition in this population. In our previous studies, WMT was shown to quickly improve gastrointestinal symptoms in various diseases, such as CDI, radiation enteritis, CD, and antibiotic-associated diarrhea [26–29]. In the current study, WMT significantly improved gastrointestinal symptoms in gastrointestinal disease–related malnourished children, including diarrhea, mucous stool, abdominal pain, hematochezia, and abdominal distention, and prevented 33.3% of mildly malnourished children from progressing to moderate-to-severe malnutrition. Abdominal distension did not improve significantly 1 mo after WMT, which requires further study.

The risk of death of malnourished children is twice as high as that of non-malnourished children [30]. When a child's weight-for-length Z-score is −2 to −1, the all-death hazard ratio is 1.6; when it falls to −3 to −2, the all-death hazard ratio increases to 3.4. Even worse, when the weight-for-length *Z*-score falls below −3, the all-death hazard ratio increases to 11.6 [31]. When children's BMIZs improve in every range, their all-death hazard ratio decreases significantly, referring to our definition of clinical response. In the WMT with EEN subgroup, there was no significant improvement in nutritional status. On the one hand, this was due to the small sample size, and on the other hand, EEN therapy is challenging in children [32], so only a few patients with the worst nutritional status and severe diseases received 3 mo of EEN. It may be difficult for their nutritional status to significantly improve within 3 mo. In the WMT subgroup, the BMIZ significantly improved, which underscores the important role of WMT in improving nutritional status. STAMP scores decreased significantly post-WMT, which indicates a synchronized reduction in the risk of malnutrition faced by the participants. There was no significant change in HAZ post-WMT, which may be due to the fact that the HAZs of the included children were mostly within the normal reference range. While for children with HAZ < -2, which was defined as chronic malnutrition, it was difficult to improve in the short term. Significantly elevated BMIZ in children with FI suggests that, by mitigating their etiology, the nutritional status of this cohort can be rapidly improved in 3 mo. However, higher-quality studies are needed to confirm this finding.

Studies have shown that serum albumin levels are the best predictor of mortality risk in malnourished children [33], and serum prealbumin levels have been positively correlated with the linear growth of children [34]. In our study, albumin and prealbumin levels significantly increased post-WMT, supporting a significant improvement in the nutritional status of malnourished children post-WMT, which is important for improving children's growth and reducing the risk of death. Possibly due to the small sample size (only four patients had below-normal hemoglobin at baseline), only a trend toward higher median serum hemoglobin levels was detected in this study, and there was no statistically significant difference—a result that must be further explored. In children with different etiologies of IBD and FI, there was a trend toward higher laboratory nutritional indicators after WMT. Still, the sample sizes were too small for statistically significant differences, and subsequent studies with larger sample sizes are needed.

There is growing evidence showing that child malnutrition is associated with gut microbiota. Huus et al. found that cross-feeding of enteric pathogens can further worsen their overgrowth in malnutrition [35]. Subramanian et al. proposed the concept of "microbiota-for-age Z-score," which suggests that child development is closely related to the maturation of gut microbes [3]. The growth of children with impaired gut microbiome maturation is far worse than the age- and sex-matched healthy children [5]. Chen et al. developed microbiota-directed complementary foods (MDCFs), aiming to improve the maturation of gut microbiota of malnourished children, and one of those (MDCF-2) significantly improved the development of malnourished children compared with ready-to-use supplementary food with the same calories [8]. Chang et al. revealed that *Prevotella copri* played a key role in the development of malnourished children treated with MDCFs. They promoted weight gain, regulated epithelial cell metabolism, and facilitated the absorption and metabolism of nutrients in intestinal epithelial cells by interacting with other microbes [36]. Other probiotics, such as *Lactobacillus rhamnosus* GG, also have been reported to be beneficial for the growth of malnourished children [37,38]. Improving the nutritional status of malnourished children post-WMT may be related to the maturation of gut microbiota and changes in microbial structure and metabolism, which need further investigation.

Consistent with previous studies [13], WMT had a high degree of safety in the current cohort. The incidence of AEs was comparable between malnourished children of different severities and routes of delivery, demonstrating that WMT has a high degree of safety. Children with FI had a relatively high incidence rate of AEs, which suggested that such children may need deeply washed fecal suspensions to improve safety, but further investigation is still needed.

IBD patients often suffer from diarrhea, malabsorption of nutrients, and other symptoms that make it difficult for them to recover from malnutrition. The American Gastroenterological Association pointed out that patients with IBD are often comorbidly malnourished, an underrecognized condition not emphasized by clinicians [39]. The double diseases burden of malnutrition and IBD can have a disproportionately negative impact on children's physical and mental health [40]. It is important for clinicians to identify malnutrition in children with IBD and intervene as early as possible. WMT may be beneficial for both malnutrition and IBD by regulating gut microbiota [28,37,38], making it a possible treatment modality for children with IBD combined with malnutrition. While failing to achieve significant improvement, there was a trend toward higher BMIZ in IBD patients after WMT, possibly due to their incurable intestinal inflammatory burden making it more difficult for them to recover from malnutrition within 3 mo, and longer follow-up is needed to determine their benefit.

This study has several limitations. First, this study's sample size was small, and studies with larger sizes and control groups are needed for further exploration. Second, 3-mo observations cannot reflect the effects of WMT on long-term growth and development in children. Studies with longer follow-ups are needed to characterize the long-term efficacy and safety of WMT for pediatric patients. Finally, we did not analyze the change in gut microbiota, so we could not explore the mechanisms of WMT.

In conclusion, this study suggests that WMT may be effective and safe for improving the nutritional status of malnourished children with gastrointestinal diseases and alleviating their symptoms at 3-mo follow-up. We found that rebuilding gut microbiota can help these children achieve growth catch-up, supporting the potential of microbiome medicine as a distinct area of clinical practice.

Declaration of competing interest

Faming Zhang conceived the concept of GenFMTer, TET, and related devices. The remaining authors declare that the research was conducted without commercial or financial relationships that could be construed as potential conflicts of interest.

CRediT authorship contribution statement

Yuyan Xiao: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xinyi He:** Writing – original draft, Investigation, Formal analysis, Data curation. **Hui Zhang:** Writing – review & editing, Investigation, Data curation. **Xia Wu:** Writing – review & editing, Supervision, Methodology. **Rujun Ai:** Writing – review & editing. **Jie Xu:** Writing – review & editing. **Quan Wen:** Writing – review & editing, Investigation. **Faming Zhang:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Bota Cui:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Availability of data and materials

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

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2024.112679.

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