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Clinical benefit of oral lactulose for postoperative care of patients with complicated appendicitis using propensity score matching analysis

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Abstract

Objective: The aim of this study was to investigate the effect of oral lactulose for pediatric patients with complicated appendicitis, who underwent appendectomy.

Background: Oral lactulose was widely used for gastrointestinal function regulation. However, clinical benefit for oral lactulose regarding its effects on recent postoperative gastrointestinal (GI) recovery and long term adhesive small bowel obstruction (ASBO) incidence, especially in the postoperative pediatric population has not yet defined.

Methods: A total of 525 pediatric patients with complicated appendicitis underwent appendectomy were retrospectively reviewed. Among them, 317 cases were subjected to oral lactulose management and 208 patients without, served as control. Propensity score 1:1 matching was carried out to adjust for any potential baseline variables. In 189 paired patients, clinical outcomes, including gastrointestinal recovery variables, incidence of ASBO, as well as adverse events, were compared according to the oral lactulose administration or not.

Results: Patients who received oral lactulose administration achieved early gastrointestinal function recovery, including, first bowel movement (Risk ratio [RR], 1.34; 95% confidence interval [CI] 1.02–2.63, $p = 0.005$) and first solid feeding (RR, 1.26; 95% CI, 1.01–1.92, $p = 0.012$). A lower occurrence of ASBO (OR, 0.47; 95% CI, 0.25–0.87; $p = 0.011$) and lower constipation (Odds ratio [OR], 0.25; 95% CI, 0.13–0.46; $p < 0.001$), were noted in patients received oral lactulose than in patients without. Furthermore, significantly fewer patients required readmission (OR, 0.56; 95% CI, 0.32–0.99; $p = 0.031$) and reoperation (OR, 0.29; 95% CI, 0.09–0.92; $p = 0.022$) in the patients who received oral lactulose administration.

Conclusions: Beneficial effects of oral lactulose administration in pediatric patients undergone appendectomy were indicated, such as accelerating gastrointestinal function recovery, reducing the postoperative incidence of ASBO and constipation, so reduced readmission and reoperation.

Keywords: Lactulose, Gastrointestinal function, Postoperative complications, Adhesive small bowel obstruction

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Background

Complicated appendicitis (periappendiceal abscess or pan-peritonitis) was associated with severe inflammatory secretion, which is the main etiologic factor for postoperative ileus (POI), and which developed with pain, nausea, vomiting, distension and the inability to take sufficient liquids and solids [1, 2]. Accelerating gastrointestinal recovery could increase patient comfort, reduce surgical complications, decrease the average hospital length of stay (LOS), and other demands on healthcare resources [3].

Core accelerated care pathways included no perioperative fasting, optimal nutrition and fluid management, decreased use of tubes, optimizing pain control, and early mobilization have been used in some specialized centers to facilitate gastrointestinal (GI) recovery [4, 5]. Furthermore, postoperative adhesive small bowel obstruction (ASBO), is the most common surgical causes for hospital readmission, bowel resection [6], but until now, no specific treatment currently exists for the treatment or prevention of POI and ASBO. Alvimopan has been suggested with possible therapeutic effect in accelerated the recovery of bowel function [7]. Sesame oil and Gastrografin has been used for postoperative ASBO though relieve constipation and keep bowel movements regular. The advantage of this treatment was effective, safe and no radiation involvement [8, 9]. The laxatives confers therapeutic benefits by guiding water into the intestinal lumen, promoting smooth muscle contractility and decreasing the intestinal edema [10]. Information for oral lactulose regarding its effects on postoperative care in pediatric populations is sparse.

In our institute, oral lactulose was prescribed in some patients according to the preference and experience of some of surgical team. We retrospectively reviewed a consecutive series of pediatric patients following appendectomy to compare the therapeutic role of oral lactulose, in terms of intestinal function recovery, and ASBO incidence.

Methods

Patients

The retrospective review was conducted with the patients underwent appendectomy for complicated appendicitis in a general surgery department of a tertiary hospital from Aug. 2013 to Aug. 2018. The hospital ethics committee for medical research of the Children's Hospital of Chongqing Medical University approved the study protocol. Consent was obtained from a parent or guardian on behalf of any participants under the age of 16. Pediatric patients undergoing emergency appendectomy, either laparoscopic or open approach, were eligible for entry into the study upon meeting the following inclusion criteria: patients age > 1 year and < 16 years;

evidence of complicated appendicitis; normal renal and hepatic function. Exclusion criteria included evidence of simple appendicitis; poor compliance of lactulose administration; previous abdominal operation; interval appendectomy; narcotic utilization for pain management; incomplete follow-up data, etc.

Managements

In our institution, complicated appendicitis was confirmed during the emergency surgical interventions, including laparoscopic or open procedures. Following the emergency surgery, all patients underwent the same postoperative programme, including enteral feeding, early ambulation and fluid resuscitation if necessary. The accelerated postoperative care protocol was used to promote the recovery of GI function. On postoperative day 1, ambulation was encouraged; liquids and solid food was offered in proper order from postoperative day 1 or day 2. If kept in place after surgery, the nasogastric tube (NGT) was removed within 24 h after surgery. Probiotics, aprocristic agents or atropine, when appropriate were symptomatically used for diarrhea and abdominal cramping or bloating. Other adverse symptoms were managed as indicated clinically. Postoperatively, all the patients were administered intravenous broad-spectrum antibiotics continuously with either piperacillin/tazobactam (100–150 mg/kg/day in two divided doses) or cefoperazone sodium/sulbactam (100–150 mg/kg/dose in two divided doses) and metronidazole (30 mg/kg/dose in two divided doses) for about 5 days until the serum C-reactive protein (CRP) concentrations decreased to below 1.0 mg/dL. Choice of lactulose depended on the patient condition and surgeon's preference, because some surgeons in our institution felt that it might be necessary and safe for lactulose administration. The lactulose was started on the first day after surgery in some patients once daily and continued for a maximum of 5 years to stimulate bowel function, if a patient did not spontaneously defaecate with 2 days. The dose of lactulose was adjusted to the target of defecate once a day.

Clinical data and outcome evaluation

Following institutional review board approval, the medical records of all included patients were thoroughly reviewed by two independent investigators who had undergone our specific training. The collected data available in the medical records included the patients' clinical history and physical examination findings on admission, like onset and course of nausea/vomiting, crampy pain, distension, fever, bowel sounds; laboratory data on admission, including venous blood leukocyte count, CRP if available and serum electrolytes prior to the oral lactulose; the original imaging examination on admission, including B ultrasound, or computed tomography (CT) scans; operative

data, like surgical approach (conventional or laparoscopic), as well as the postoperative outcomes, including gastrointestinal symptoms (first bowel movement [gas and feces] after operation, abdominal bloating, abdominal cramps, diarrhea [defined as more than three bowel movements per day], and vomiting), intra-operative microbiological data, infectious complications (wound infection or granuloma, peritonitis or abscess). Obstruction event was defined as nausea, vomiting or abdominal pain lasting less than 3 days after the operation. Prolonged ileus was defined as a sustained non-mechanical obstruction lasting more than 5 days after the operation and confirmed by simple abdominal radiography.

Follow up

In our institute, all patients were systematically followed up through telephone call at 6, 12 and 24 months by the investigators. Some patients were followed at the outpatient clinic at which time the questionnaire for postoperative symptoms were filled out. The date and type of obstruction event managed in the same or in another surgical unit were also collected. Twenty-seven patients (9%) were lost to follow-up and two third over 2 years of follow-up. The ASBO readmission were defined as the hospital admission for presence of abdominal pain and distention, vomiting, and complete constipation (gas and feces), which were confirmed by the abdominal film.

The primary outcome measure was the incidence of readmission for ASBO. the time span of readmission was measured from the day of the primary operation to the readmission. The acute adhesive small bowel obstruction (ASBO) episode was defined as an admission to hospital for a patient already undergone abdominal surgery in the past, with the following diagnostic criteria: presence of abdominal pain, vomiting, complete constipation (gas and feces), or the attending surgeon giving the diagnosis of acute ASBO. Secondary outcomes included the GI function recovery variables, including first bowel movement, postoperative solid feeding time, the perioperative complications, and hospital LOS (the total number of days from the admission to discharge), etc.

Statistical analysis

As potential confounders could affect the readmission for obstruction and lactulose was not used in a randomized manner in our study, we established propensity score matching using SPSS 20.0 (IBM, Armonk, NY) or R 3.1.2 (The R Foundation for Statistical Computing) to avoid the potential confounders. A 1:1 Propensity scores matching was performed using the nearest neighbor without replacement matching algorithm and a 0.1 caliper width. The generalized additive model was used to check linear assumption in PS model. After PS matching, statistical comparisons were conducted between the matched

lactulose treatment patients and controls using SPSS 20.0 (IBM, Armonk, NY). Continuous data were expressed as means \pm SDs or median (interquartile range [IQR]) and were analyzed using Student's t-test or Mann-Whitney U test respectively. The discrete variables was analyzed by a chi-square test or Fisher's exact test, and then by estimation of the relative risk between treatment groups. The relative risks for postoperative variables were assessed using cross-tabulation (odds ratio [OR]) or multivariate logistic regression analysis (risk ratio [RR]). The statistical significance was evaluated using a two-tailed 95% confidence interval (CI), and statistical significance was established if $P < 0.05$.

Results

Patient characteristics

Among the initial 525 pediatric patients eligible for analysis, 317 (60.4%) received postoperative laxative administration. The baseline features of the patients according to laxative administration are summarized in Table 1. Before PS-matching, there were no significant differences in terms of age, sex, laboratory test (like, white blood cell counts, CRP concentrations), duration of symptoms on admission between the two groups, suggesting that there were no systematic differences in baseline characteristics between the two groups. Under PS-matching, 189 patients with laxative administration were matched to 189 patients without. There were no significant differences in surgical approach between the two groups with unmatched and propensity score matched patients (Table 1). Several variables, including operation type, became more comparable after PS-matching (Table 1). Under PS-matching, the absolute standardized mean differences reduced the values to the range from 0.01 to 0.07, indicating that the continuous and categorical variables were very similar and comparable between the patients with and without laxative administration (Table 1).

Efficacy for gastrointestinal function recovery

A positive trend for accelerated GI function recovery was observed for patients treated with laxative, which was assessed by first bowel movement, first stool, and postoperative feeding time. The first bowel movements occurred 1.6 ± 0.6 days and 2.2 ± 0.8 days after surgery in the patients with and without laxative treatment, respectively (Risk ratio [RR], 1.34; 95% confidence interval [CI] 1.02–2.63, $p = 0.005$). The first solid feeding is faster in the patients with laxative treatment than without (RR, 1.26; 95% CI, 1.01–1.92, $p = 0.012$), whereas no difference was found for first flatus ($p = 0.082$). In the successful laxative treated cases, 77.8% (137/189) patients with oral laxative treatment spontaneously passed stool within 72 h, whereas only 47.1% (121/189)

Table 1 Baseline demographics and preoperative variables of eligible population

Lactulose	Total population			Propensity matched population		
	With (317)	Without (208)	<i>P</i> Values	With (189)	Without (189)	<i>P</i> Values
Age (yrs), Mean ± SD	6.2 ± 1.8	6.1 ± 1.7	0.19	6.1 ± 1.7	6.1 ± 1.8	0.33
Male: female	186:131	120:88	0.45	108:81	109:80	0.50
Mean body weight (kg), Mean ± SD	13.9 ± 5.7	13.8 ± 5.8	0.36	13.8 ± 5.4	13.8 ± 5.2	0.62
WBC (10 ⁹ /L), Mean ± SD	17.5 ± 4.9	18.2 ± 5.2	0.24	17.6 ± 4.5	17.9 ± 4.9	0.39
PCT (ng/ml, normal value: 0–0.5)	6.7 ± 2.1	6.9 ± 2.2	0.33	6.8 ± 2.0	6.8 ± 2.1	0.52
CPR (mg/L, normal value: 0–10)	14.1 ± 4.9	13.9 ± 4.7	0.18	14.0 ± 4.2	13.9 ± 4.3	0.36
Duration of symptoms on admission (h), days, Mean ± SD	2.7 ± 1.4	2.9 ± 1.6	0.26	2.8 ± 1.5	2.8 ± 1.6	0.38
Clinical symptoms, N (%)						
Abdominal pain	294 (92.7)	193 (92.8)	0.57	175 (92.6)	175 (92.6)	0.58
Vomiting	183 (57.7)	122 (58.7)	0.45	109 (57.7)	110 (58.2)	0.50
Fever	152 (47.9)	98 (47.1)	0.46	90 (47.6)	90 (47.6)	0.50
Appendicolith	113 (35.6)	66 (31.7)	0.20	64 (33.9)	62 (32.8)	0.46
pan-peritonitis	82 (25.9)	57 (27.4)	0.39	50 (26.5)	51 (27.0)	0.50
Abscess 2 cm or more, N (%)	63 (19.9)	42 (20.2)	0.51	38 (20.1)	38 (20.1)	0.55
Operation type, N (%)						
Laparoscopical	193 (60.9)	127 (61.1)	0.52	115 (60.8)	116 (61.4)	0.50
Open	124 (29.1)	81 (28.9)		74 (29.2)	73 (28.4)	

Abbreviation: WBC white blood cell, PCT procalcitonin, CRP C-reactive protein

cases in the control group passed stool within the same duration (RR, 1.48; 95%CI 0.96–2.29, $p = 0.049$). There were no differences in the incidence of diarrhea or serum electrolyte abnormalities between the two groups. The mean length of hospital stay was 8.9 ± 1.7 days in patients receiving laxative, which was significantly less than the mean length of stay (9.7 ± 1.6 days) in patients without laxative treatment (RR, 0.54; 95% CI, 0.32–0.98, $p = 0.038$) (Table 2).

Follow-up and recurrence rates

The median follow-up was 31 months (range, 12–89 months). During follow-up, the incidence of constipation

in the patients with oral laxative administration was significantly lower compared with that in the control (OR, 0.25; 95% CI, 0.13–0.46; $p < 0.001$), which was expected. The most common reasons for the hospital readmission were surgery related ABSO. Significant less incidence of ASBO was observed in the patients who received laxative (OR, 0.47; 95% CI, 0.25–0.87; $p = 0.011$) compared with the control (Table 3). Among them, the median time of first recurrent ASBO was 3.6 months for laxative group and 2.8 months for control after operation. Of those patients who received laxative, 22 cases (11.6%) of patients within 24 months were readmitted to the hospital for ABSO and 36 cases (18.5%) of patients

Table 2 Gastrointestinal function and early outcome in the matched population

Lactulose	With (189)	Without (189)	<i>P</i> values	Risk ratio (95% CI)
First flatus, days, Mean ± SD	2.1 ± 0.9	2.5 ± 1.1	0.082	1.19 (0.83–1.69)
first bowel movement, Mean ± SD	1.6 ± 0.6	2.2 ± 0.8	0.005	1.34 (1.02–2.63)
passed stool within 72 h, N (%)	137 (72.5)	121 (64.0)	0.049	1.48 (0.96–2.29)
Postoperative NGT, N (%)	28 (14.8)	39 (20.6)	0.089	0.67 (0.39–1.14)
x-ray measurement, N (%)	36 (19.0)	50 (26.5)	0.055	0.65 (0.40–1.06)
First solid feeding, days, Mean ± SD	2.0 ± 0.4	2.6 ± 0.5	0.012	1.26 (1.01–1.92)
Obstruction event, N (%)	71 (37.6)	57 (30.2)	0.13	1.39 (0.91–2.14)
Abdominal distension after POD 5, N (%)	39 (20.6)	47 (24.9)	0.20	0.79 (0.49–1.27)
CRP at POD 5, mg/L, Mean ± SD	22.2 ± 6.7	26.6 ± 7.3	0.053	0.72 (0.53–1.97)
Postoperative hospital stay, days, Mean ± SD	8.9 ± 1.7	9.7 ± 1.6	0.038	0.54 (0.32–0.98)

Abbreviation: NGT nasogastric tube, POD postoperative day

Table 3 Follow-up and recurrence rates in the matched population

Lactulose	With (189)	Without (189)	P Values	Odds ratio (95% CI)
constipation, N (%)	15 (7.9)	49 (25.9)	< 0.001	0.25 (0.13–0.46)
incidence of prolonged POI, N (%)	28 (14.8)	37 (19.6)	0.14	0.71 (0.42–1.22)
incidence of ASBO	17 (9.0)	33 (17.5)	0.011	0.47 (0.25–0.87)
time of first recurrent ASBO, month, median (range)	3.6 (2.5–12)	2.8 (1.7–15)	0.12	
Hospital readmission, N (%)	22 (11.6)	36 (18.5)	0.031	0.56 (0.32–0.99)
re-operation for ASBO, N (%)	4 (2.1)	13 (5.8)	0.022	0.29 (0.09–0.92)
Bowel resection	2 (1.1)	6 (3.2)	0.14	

Abbreviation: POI postoperative ileus, ASBO adhesive small bowel obstruction

in the control, suggesting that laxative reduced the need for hospital readmission (OR, 0.56; 95% CI, 0.32–0.99; $p = 0.031$). Of the 17 patients who required surgical intervention, four patients (2.1%) with laxative were subjected with emergency surgery and 11 (5.8%) control patients had re-operation (OR, 0.29; 95% CI, 0.09–0.92; $p = 0.022$) for suspected bowel strangulation (Table 3). The bowel strangulation segments were underwent resection in 2 cases in laxative group, and 6 cases in the control.

Safety assessments

In general, oral laxative was well tolerated with similar safety profiles among oral laxative administration and control groups. The patients using laxative suffered almost equal early postoperative complications in terms of anastomotic leakage, incision dehiscence, wound infection, intraperitoneal abscess, etc. Postoperative total adverse events (AEs), like nausea or vomiting, abdominal cramps, and abdominal distention in the two groups were comparable (Table 4). Nausea and vomiting were the most common AEs that led to study discontinuation. About 18 patients (9.5%) should shortly discontinue the laxative administration by the nausea and vomiting. Furthermore, there was no difference in the incidence of diarrhea and serum electrolyte abnormalities between the two groups.

Discussion

After propensity score matching of heterogeneity in the population, the current analysis verified that oral laxative significantly accelerated GI function (bowel movements) recovery in patients undergoing appendectomy. Laxative also significantly accelerated the toleration of oral feed, which is important for hospital discharge. Furthermore, patients with the laxative administration experienced low incidence of readmission and reoperation because of the ASBO, which is a clinically important adverse event for the current surgery.

Postoperative intestinal recovery serves as the main focus of abdominal surgery [11, 12]. Postoperative ileus detention might lead to oral nutrition delay, prolonged hospital stay, even with hospital readmission [13]. Various protocols, including minimally invasive surgical intervention (eg, laparoscopy instead of laparotomy), early oral nutrition, and physical rehabilitation have been suggested to accelerate postoperative GI recovery [14, 15]. Laxatives have also been studied with significantly earlier bowel function recovery in patients undergoing hysterectomy in a randomized study [10]. The presence of laxative could promote shifting of fluid into the intestinal lumen, which might stimulate bowel activity for proper intestinal function recovery [16]. The current analysis confirmed that laxative significantly increased the proportion of

Table 4 Postoperative complication and treatment-emergent adverse events in the matched population

Lactulose	With (189)	Without (189)	P Values	Risk ratio (95% CI)
Total complications (at least 1 complication), N (%)	44 (23.3)	39 (20.6)	0.31	1.17 (0.72–1.90)
Anastomotic leakage, N (%)	2 (1.1)	1 (0.5)	0.50	2.01 (0.18–22.36)
Incision dehiscence, N (%)	6 (3.2)	7 (3.7)	0.78	0.85 (0.28–2.59)
Peritonitis or abscess, N (%)	26 (13.8)	31 (16.4)	0.28	0.81 (0.46–1.43)
Total AEs, N (%)	75 (39.7)	86 (45.5)	0.25	0.79 (0.52–1.19)
Nausea or Vomiting, N (%)	35 (18.5)	31 (16.4)	0.59	1.16 (0.68–1.97)
Abdominal cramps, N (%)	27 (14.3)	25 (13.2)	0.44	1.09 (0.61–1.96)
Diarrhea, N (%)	33 (17.5)	26 (13.8)	0.32	1.33 (0.76–2.32)
Serum electrolyte abnormalities, N (%)	15 (7.9)	18 (9.5)	0.36	0.82 (0.40–1.68)

Abbreviation: AEs adverse events

patients who achieved GI function recovery during the early recovery periods in the pediatric patients with complicated appendicitis who underwent appendectomy. Our analysis involves laxative usage in a closely monitored hospital setting, with frequent nursing assessments and continuous intestinal function monitoring. Therefore, the clinically significant intestinal complaints would likely be captured. We found that laxative usage was associated with shifting more patients into the earlier phase of the recovery process. In our institute, an accelerated care protocol was encouraged to facilitate GI recovery, including early oral nutrition and ambulation in patients undergoing major intestinal surgery. This practice not only accelerated GI recovery but resulted in shorter LOS compared with traditional care. However, the length of hospital stay for the laxative group in this analysis was indeed less than the balanced control. Therefore, the benefits of laxative were beyond those provided by accelerated postoperative care pathways alone.

According to previous reports, readmission within 30 days was required for about 3.7% of patients following the appendectomy and 7.7% (666/8688) for patients with perforated appendicitis [17]. Under our management protocol, the overall need for readmission was lower in the laxative administration patients compared with the control. Accordingly, the current laxative administration reduces the need for surgical intervention in adhesive small bowel obstruction, which has not been reported in the literature before. Previous report suggested that ranged from 6 to 11% of ASBO might develop to bowel strangulation [18, 19]. In the current study, the overall strangulation rate was only 0.8% for patients with laxative administration. We believe that beside its osmotic nature, other mechanisms may be involved in the current performance of laxative. Laxative may also reduce the inflammatory response of postoperative gastrointestinal tract, which was characteristic by edema and inflammation [20, 21], and thereby reduce ASBO. In the current research, CRP enhanced quickly following the operation and recovered better with laxative administration compared with the control, confirm the dampening of local inflammation by laxative, which might explain the current clinical results, although the exact mechanism is difficult to determine in this clinical setting.

In theory, stimulation of the bowel might cause bowel strangulation or anastomotic dehiscence [22]. But in the present study, there was no complication or mortality that could be attributed to the laxative usage. The incidence of bowel strangulation or anastomotic leak was comparable for the two groups, supporting the point that promoting GI recovery by laxative should not compromise with postoperative complications. There

was also no evidence that the use of laxative would increase the risk of nausea, abdominal cramps. Because of the fluid shifting into bowel lumen, it may further dehydrate the patient following the adverse effect of obstruction [23, 24]. The oral laxative is very little absorption making this drug quite safe to use even for a long time. In fact, adverse effects for laxative usage in small bowel obstruction have rarely been mentioned, including serum electrolyte abnormalities and other adverse events. Furthermore it is important for controlled diet and the rehabilitation treatment for the canalization, which should be preceded by re-educative treatment [25].

There are several limitations to our study, while it is the largest reported series of patient with oral laxative usage following major gastrointestinal surgery. First, this is a single-center retrospective study. The decision to initiate laxative was not made randomly with inherent risk of selection bias. The GI-associated intestinal function, like the days to defecation, first flatus and cramps were extracted from clinical records of patient, which should not be fully objective and accurate. We could not completely avoid variables that may have affected our results as residual confounders. Therefore, our results should be interpreted cautiously. Another point is that the patients with laxative administration might be more surgically challenged than the control, with more potential SBO. To avoid this, we performed propensity score matching analysis to generate comparison confounding variables on the actual effects of laxative.

Conclusion

The present data suggested that oral laxative accelerated GI recovery and reduced postoperative morbidity and readmission after appendectomy in the pediatric patients with complicated appendicitis. We acknowledge that these results are based on retrospective review of the homogenous group of patients. Thus, further trials with large patient samples randomized controlled clinical trials are required to confirm these effects.

Abbreviations

AEs: Adverse events; ASBO: Adhesive small bowel obstruction; CI: Confidence interval; CRP: C-reactive protein; CT: Computed tomography; GI: Gastrointestinal; IQR: Interquartile range; LOS: Hospital length of stay; NGT: Nasogastric tube; OR: Odds ratio; POI: Postoperative ileus; RR: Risk ratio

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Authors' contributions

XD, LQ designed the study and analyzed the data. BC and JL evaluated the manuscript. CG and BC performed the statistical measurement and analyzed the data. CG analyzed the data and wrote the paper. All authors have read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Availability of data and materials

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

Ethics approval and consent to participate

This study was approved by the ethics committee of Chongqing Medical University, and was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983. All the patients enrolled were comprehensively informed, and written informed consent to participate in this research and publish the data were obtained. Consent was obtained from a parent or guardian on behalf of any participants under the age of 16.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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