



Short-term safety and efficacy of peroral endoscopic myotomy for the treatment of achalasia in children

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Abstract

Background Peroral endoscopic myotomy (POEM) has shown excellent results for the treatment of achalasia in adults, but studies for children are limited. The study was aimed to analyze outcomes of peroral endoscopic myotomy (POEM) in children and compared with those in adults in a large multi-center study.

Methods Records of consecutive patients with achalasia who underwent POEM at three tertiary centers were reviewed. A total of 130 children were included in this study. The primary outcomes of perioperative outcomes and clinical follow-up data were analyzed.

Results One child (0.8%) experienced technical failure. Five children (3.8%) had major adverse events, including one with pneumothorax requiring drainage, two with delayed mucosa barrier failure, one with readmission, and

one with vital-sign instability. Both post-POEM Eckardt score and median LES pressure were significantly lower than their pre-POEM reference values in children (0.7 vs 7.4; 7.0 vs 27.1 mmHg; both $P < 0.001$). During a median follow-up time of 40 months, clinical reflux rate was 27.0% and clinical failure rates at 1, 3, and 5 years were 1.8%, 3.5%, and 4.4% for children. The technical failure, major adverse events, and postoperative clinical reflux were comparable between children and adults (all $P > 0.05$). Kaplan–Meier analysis showed that the risk of clinical failure was lower in children than adults (log-rank test, hazard ratio = 0.37, 95% confidence interval 0.15–0.91, $P = 0.023$).

Conclusions POEM can be safely performed in children with achalasia, and produce a better clinical response during long-term follow-up compared with that in adults.

Keywords POEM · Achalasia · Children · Outcome

Zuqiang Liu, Yun Wang, Ying Fang and Ying Huang shared co-first authorship.

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Abbreviations

POEM	Peroral endoscopic myotomy
LES	Lower esophageal sphincter
mAEs	Major adverse events
EGD	Esophagogastroduodenoscopy
CO ₂	Carbon dioxide
ICU	Intensive care unit
rePOEM	Repeat POEM

Introduction

Achalasia is a rare primary esophageal motility disorder caused by neuromuscular dysfunction in the esophago-gastric junction [1]. The incidence of esophageal

achalasia in children is estimated to be 0.02–0.31 per 100,000 children per year or nearly 10 times less than that in adults [2–4]. Children with achalasia are usually misdiagnosed and may receive delayed treatment. The main symptoms include dysphagia, regurgitation, chest pain, heartburn, and weight loss [5, 6]. The traditional management of children with achalasia includes medication, endoscopy, and Heller surgery.

Peroral endoscopic myotomy (POEM) is a minimally invasive procedure that has recently gained wide acceptance for treating achalasia in adults [7]. Although it has excellent outcomes in adults, the procedure has only recently been applied in pediatric surgical and gastroenterology practices. Studies about safety and efficacy of POEM for children are extremely limited, all of them less than 30 cases [5, 8–12]. Therefore, the aim of this study was to comprehensively evaluate and analyze the short-term and long-term outcomes of POEM in children and compared with those in adults.

Methods

Patients

This multi-center study reviewed records of all children patients with esophageal achalasia who underwent POEM from August 2010 to December 2015 at Zhongshan Hospital (Shanghai, China), December 2013 to August 2017 at Children's Hospital of Xi'an City (Xi'an, China), and December 2014 to March 2016 at Children's Hospital, Fudan University (Shanghai, China). Pediatric patients were considered ≤ 17 years of age. Children patients included in previously published studies were shown in Supplemental Table 1 [5, 8, 13]. Records of consecutive adult patients with esophageal achalasia were also reviewed as control group, who underwent POEM from August 2010 to December 2015 at Zhongshan Hospital (Shanghai, China). Exclusion criteria included coagulopathy and systemic disorders that precluded safe general anesthesia.

The achalasia was diagnosed by Eckardt score ≥ 4 [14]. The Eckardt score is the sum of the symptom scores for dysphagia, regurgitation, chest pain, and weight loss. The symptoms were recorded from the patient's self-report or the report of parents or caretakers. Besides the Eckardt score, patients with achalasia were further confirmed by barium swallow, high-resolution manometry (HRM), and esophagogastroduodenoscopy (EGD) (Supplemental Figs. 1, 2, 3a). Patients less than 3-year-old who could not complete the HRM were confirmed by barium swallow and EGD. Other preoperative demographic and clinical information included disease duration, sigmoid esophagus, prior

treatment, residual contents, mucosal edema, and submucosal fibrosis. This retrospective study was approved by the local ethics committee (ethics number: 2010-135). Written informed consent was obtained before POEM from patients or their caretakers if patients were < 16 years of age.

POEM procedure

All patients underwent general anesthesia and endotracheal intubation. Prophylactic antibiotics were delivered 30 min before the procedure and were terminated the second day after the operation. A standard procedure was followed as previously described [5, 15]. Generally, this procedure included four major steps: (1) submucosal injection and mucosal incision; (2) submucosal tunneling; (3) myotomy, from 2 cm proximal to mucosal entry to at least 2 cm below the cardia; and (4) closing mucosal entry. The representative endoscopic images of infants before, after and during POEM procedure were shown in Supplemental Fig. 3a–f. The posterior approach was generally applied except some complicated cases, such as fibrosis of the posterior location. For patients who previously received Heller myotomy or RePOEM, the tunnelling and myotomy were located in an area of normal (fibrosis-free) tissue to avoid the fibrosis or adhesions from prior treatment [16].

Patients fasted until the evening of the first postoperative day. After that, liquid was allowed if patients recovered well. Room air insufflation was initially used during the procedure before December 2011 and was subsequently replaced by carbon dioxide (CO₂) in Zhongshan Hospital, Fudan University. For other two children's hospitals, carbon dioxide was used for all patients.

Instruments

Instruments for pediatric patients were the same as those for adults. A high-definition endoscope was applied in all cases (GIF-H260 or GIF-Q260; Olympus Medical Systems Co, Tokyo, Japan). A transparent cap was taped to the top of the gastroscope (D-201-11802; Olympus). Other equipment included a hybrid knife (ERBE, Erbe Elektromedizin GmbH, Tübingen, Germany), hook knife (KD-620LR; Olympus), triangle-tip knife (KD-640L; Olympus), hot biopsy forceps (FD-410LR; Olympus), injection needle (NM-4L-1; Olympus), clips (HX-610-90, HX-600-135; Olympus; Resolution, Boston, Mass), argon plasma coagulation unit (APC300; ERBE), and high-frequency generator (VIO 200D; ERBE).

Outcome measures

Perioperative outcomes and clinical follow-up were evaluated. Perioperative outcomes included technical failure

and perioperative major adverse events (mAEs). Technical failure was defined as the inability to finish the procedure after submucosal injection [17]. mAEs were defined as vital-sign instability, blood transfusion, post-procedure intensive care unit (ICU) stay, conversion to laparoscopic or open procedure, postoperative invasive operation, hospital stay longer than 5 days due to functional impairment, and hospital readmission after discharge [18]. Clinical follow-up outcomes included clinical reflux and clinical failure. Clinical reflux included symptomatic reflux and reflux esophagitis and was diagnosed by either positive result. Symptomatic reflux was defined by the GerdQ questionnaire [16, 19], which is based on six items related to gastroesophageal reflux disease, including four positive predictors (i.e., heartburn, regurgitation, sleep disturbance due to these two reflux symptoms, and use of over-the-counter medication in addition to prescribed medication) and two negative predictors (i.e., epigastric pain and nausea). Reflux esophagitis was diagnosed and graded by EGD based on Los Angeles (LA) Classification. Clinical failure was defined as a postoperative Eckardt score ≥ 4 [20].

Follow-up

Patients received regular follow-up postoperatively at 1 month, 3 months, 6 months, 1 year, and yearly thereafter. For very young patients, follow-up was performed by their patients of caretakers. Eckardt score was obtained to evaluate clinical response. Barium swallow was performed to objectively evaluate treatment efficacy and clinical response. EGD was regularly performed for both outcome evaluation and cancer screening. HRM was also strongly suggested, especially for patients with dysphagia. Patients or caretakers living a long distance from the hospital or unwilling to return for follow-up were followed through detailed telephone interviews, including questions about their symptoms and examinations and treatments at other hospitals. The most recent follow-ups were performed in December 2017.

Statistical analyses

Patient and procedural characteristics, technical failure, mAEs, and clinical follow-up data were compared between adult and pediatric patients. Categorical variables were compared using Chi square or Fisher's tests, and continuous variables were compared using Student *t* tests or ANOVA. Kaplan–Meier analysis was performed to evaluate variables associated with long-term clinical failure using the log-rank test. Statistical significance was considered as two-sided $P < 0.05$. Statistical analysis was performed using the SPSS software package (version 21.0, SPSS Inc., Chicago, IL, USA).

Results

Patient and procedural characteristics of children

Patient and procedural characteristics of children are shown in Table 1. A total of 130 patients of children were included in this study, including 87 patients from Zhongshan Hospital, 25 from Children's Hospital of Xi'an City, and 18 from Children's Hospital, Fudan University. Median ages were respectively 14, 7.7, and 7.5 for Zhongshan Hospital, Children's Hospital of Xi'an City, and Children's Hospital, Fudan University. Median disease durations were, respectively, 1, 0.75, and 1.1 of Zhongshan Hospital, Children's Hospital of Xi'an City, and Children's Hospital, Fudan University. No positive result of family history was found in the children. Twelve children had certain past and/or present history of autoimmune diseases, including six urticaria, four eczema, one asthma, and one ankylosing spondylitis. Eighty-two of the 130 patients (63.1%) were male. One hundred and twelve patients underwent HRM, including 40 patients of Type I (35.7%), 65 patients of Type II (58.0%), and 7 patients of Type III (6.3%). Eighteen patients did not have information of HRM, including 9 patients less than 3-year-old who could not complete the HRM. Mean preoperative Eckardt score and median lower esophageal sphincter (LES) pressure were 7.4 ± 1.9 and 27.1 mmHg ($15.0\text{--}66.5 \text{ mmHg}$), respectively. The median disease duration was 1 year (range 0–13 year). Four patients (3.1%) had developed sigmoid esophagus. Twenty patients (15.4%) had undergone prior treatments, including 12 patients with dilation, three patients with stent, one patient with Botulinum toxin injection, three patient with Heller myotomy and one patient with POEM. Mucosal edema occurred in nine patients (6.9%) and submucosal fibrosis occurred in five patients (3.8%).

CO₂ insufflation was used for 112 patients (86.2%), while 18 patients (13.8%) received air insufflation. Full-thickness myotomy was performed in 103 patients (79.8%). Lengths of esophageal tunneling and myotomy were 9.2 ± 1.3 and 7.2 ± 1.4 cm, respectively. Median procedure time and length of hospital stay were 30 (15–255) minutes and 3 (1–21) days, respectively. One hundred and twenty-three children (94.6%) had the operation performed by doctor experienced with more than 100 cases.

Table 2 shows detailed characteristics of children stratified by age groups: 0–6, 7–12, and 13–17 years of age. Sixty-four (49.2%) pediatric patients were 13–17 years old, 46 (35.4%) were 7–12 years old, and 20 (15.4%) were 0–6 years old. The youngest child was 11 months old. Older children had longer lengths of esophageal tunneling and myotomy and a shorter hospital stay (all $P < 0.001$). Other patient and procedural

Table 1 Patient and procedural characteristics in children

Variables	Number
Patient characteristics	
Total number	130
Male, <i>n</i> (%)	82 (63.1%)
Pre-POEM Eckardt score, mean \pm SD	7.4 \pm 1.9
Pre-POEM resting LES pressure, median (range), mmHg	27.1 (15.0–66.5)
Achalasia subtype*, <i>n</i> (%)	
Type I	40 (35.7%)
Type II	65 (58.0%)
Type III	7 (6.3%)
Disease duration, median (range), years	1 (0–13)
Sigmoid esophagus	4 (3.1%)
Prior treatments	20 (15.4%)
Residual contents	8 (6.2%)
Mucosal edema	9 (6.9%)
Submucosal fibrosis	5 (3.8%)
Procedural characteristics	
CO ₂ insufflation	112 (86.2%)
Full-thickness myotomy	103 (79.8%)
Length of esophageal tunneling, mean \pm SD, cm	9.2 \pm 1.3
Length of gastric tunneling, mean \pm SD, cm	3.0 \pm 0.3
Length of esophageal myotomy, mean \pm SD, cm	7.2 \pm 1.4
Length of gastric myotomy, mean \pm SD, cm	2.2 \pm 0.5
Procedure time, median (range), minutes	30 (15–255)
Hospital length of stay, median (range), days	3 (1–21)
Doctor experience > 100 cases	123 (94.6%)

POEM peroral endoscopic myotomy, SD standard deviation, LES lower esophageal sphincter

*Achalasia subtype was unspecified in 18 patients

characteristics including insufflation, full-thickness, length of gastric myotomy and tunneling, doctor experience, and procedure time were comparable between the three age groups (all $P > 0.05$).

Perioperative outcome evaluation in children

No perioperative death occurred in the study. One child (0.8%) experienced technical failure, who had undergone dilatation prior to POEM (Table 3). Technical failure was mainly due to serious submucosal inflammation and adhesion. The patient received repeat POEM (rePOEM) and relieved during follow-up. Only five of the 130 children (3.8%) had mAEs, including one (0.75%) with pneumothorax requiring drainage, two (1.5%) with delayed mucosa barrier failure, one (0.75%) with readmission, and one (0.75%) with vital-sign instability. One patient was readmitted after discharge because of severe chest pain. No positive complication was found by EGD or CT scan. The patient was then discharged after supportive therapy and observed for several days. Cerebral ischemia happened for

another patient with vital-sign instability after POEM. The patient survived but got brain impairment, including intelligence, listening, and body movement disorders. The patients received functional training in the later year and recovered to some degree. Other patients recovered by conservative or endoscopic treatments and no patient received conversion to laparoscopic or open procedure. Detailed information on technical failure and mAEs is provided in Supplemental Table 2.

Postoperative clinical reflux in children

Nine patients 3-year-old were excluded from symptomatic reflux evaluation as the patients or caretakers could not answer the GerdQ questionnaire. Among the 9 patients, two patients without postoperative EGD were excluded from GERD evaluation. As a result, evaluation of postoperative GERD and symptomatic reflux was available for 111 and 104 children, respectively. Thirty patients (30/111, 27.0%) had signs of clinical reflux, including either symptomatic reflux or reflux esophagitis. Symptomatic

Table 2 Patient and procedural characteristics in children categorized by age

Variables	0–6 years	7–12 years	13–17 years	<i>P</i>
Patient characteristics				
Total number	20	46	64	
Male gender, <i>n</i> (%)	11 (55.0%)	30 (65.2%)	41 (64.1%)	0.730
Pre-POEM Eckardt score, mean ± SD	7.8 ± 1.5	7.2 ± 1.9	7.4 ± 1.9	0.539
Pre-POEM resting LES pressure, median (range), mmHg	28.2 (17.1–50.5)	26.3 (15.0–63.2)	34.8 (15.0–66.6)	0.140
Achalasia subtype*, <i>n</i> (%)				0.774
Type I	4 (36.4%)	14 (33.3%)	22 (37.3%)	
Type II	6 (54.5%)	24 (57.1%)	35 (59.3%)	
Type III	1 (9.1%)	4 (9.5%)	2 (3.4%)	
Disease duration, median (range), year	1 (0–2)	1 (0.1–9)	1.5 (0.11–3)	0.110
Sigmoid esophagus	1 (5.0%)	1 (2.2%)	2 (3.1%)	1.000
Prior treatment	2 (10.0%)	9 (19.6%)	9 (14.1%)	0.608
Residual contents	1 (5.0%)	4 (8.7%)	3 (4.7%)	0.633
Mucosal edema	1 (5.0%)	3 (6.5%)	5 (7.8%)	1.000
Submucosal adhesion	0	3 (6.5%)	2 (3.1%)	0.570
Procedural characteristics				
Insufflation, air	1 (5.0%)	4 (8.7%)	13 (20.3%)	0.089
Full thickness	15 (75.0%)	37 (82.2%)	51 (79.7%)	0.799
Length of esophageal tunneling, mean ± SD, cm	7.9 ± 1.8	9.1 ± 1.3	9.6 ± 0.8	< 0.001
Length of gastric tunneling, mean ± SD, cm	3.0 ± 0.2	3.0 ± 0.4	3.0 ± 0.2	0.456
Length of esophageal myotomy, mean ± SD, cm	5.7 ± 1.8	7.1 ± 1.3	7.7 ± 1.0	< 0.001
Length of gastric myotomy, mean ± SD, cm	2.1 ± 0.7	2.2 ± 0.5	2.2 ± 0.4	0.425
Doctor experience > 100 cases	20 (100%)	45 (97.8%)	58 (90.6%)	0.212
Procedure time, median (range), minutes	30 (20–47)	27 (18–255)	35 (15–113)	0.488
Hospital length of stay, median (range), days	9 (3–21)	3 (1–18)	2 (1–6)	< 0.001

POEM, peroral endoscopic myotomy; SD, standard deviation; LES, lower esophageal sphincter. *Achalasia subtype was unspecified in 18 patients

reflux occurred in 15 patients (15/104, 14.4%). Sixty-six children received postoperative EGD, of whom reflux esophagitis was confirmed in 25.8% of patients (17/66). Most children (80.0%) had LA Grade A esophagitis, with no occurrences of LA grade D esophagitis (Table 4). Detailed information on clinical reflux is provided in Supplemental Table 2. Once diagnosed with clinical reflux, PPIs were applied half hour before breakfast in children with omeprazole 0.7–3.5 mg/kg per day for 12 weeks [21, 22]. For adolescent patients (12–17 years old), the algorithm of adult GERD treatment could be applied [23]. All patients relieved during follow-up and no patient received invasive intervene.

Clinical failure in children

Of the 130 patients, 17 (13.1%) were lost to clinical follow-up. Among the 113 patients with follow-up, the median follow-up time was 40 (4–88) months. Clinical failure

occurred in five patients (4.4%) during follow-up (Table 4). Both post-POEM Eckardt score and median LES pressure were significantly lower than their pre-POEM reference values (0.7 vs 7.4, 7.0 vs 27.1, both $P < 0.001$). Clinical failure rates at 1, 2, 3, 4, 5, and 6 years were 1.8%, 1.8%, 3.5%, 4.4%, 4.4%, and 4.4%. Detailed information on clinical failure is provided in Supplemental Table 2. One pediatric patient who received prior treatment of dilation had a perioperative mAE of readmission and clinical failure 10 months after the procedure. All children with clinical failure received rePOEM and experienced relief during follow-up.

Comparison of outcomes between children and adults

A total of 1749 patients of adults were included in this study. Comparison of patient and procedural characteristics between children and adults is shown in Supplemental

Table 3 Technical failure and major adverse events in children

Variables	Number
Technical failure	1 (0.8%)
Major adverse events	5 (3.8%)
Pneumothorax requiring drainage	1 (0.75%)
Delayed mucosa barrier failure	2 (1.5%)
Readmission	1 (0.75%)
Vital-sign instability	1 (0.75%)

Table 4. The children group consisted of a larger proportion of males with a shorter disease duration, less sigmoid esophagus, and less prior treatment ($P = 0.002$, < 0.001 , $= 0.042$, and $= 0.006$, respectively). Children had a shorter procedure time (30 vs. 45 min, $P < 0.001$) and longer hospital stay (3 vs. 2 days, $P < 0.001$) compared with adults. Lengths of esophageal tunneling and myotomy were shorter in children than in adults ($P < 0.001$ and < 0.001 , respectively). Other patient and procedural characteristics were comparable between children and adults (all $P > 0.05$).

Comparison of outcome evaluation between children and adults is shown in Table 5. Perioperative outcomes, including technical failure and mAEs, showed no significant difference between children and adults ($P = 1.000$, $P = 0.795$, respectively). The median follow-up time was

comparable between children and adults (40 vs. 45 months, $P = 0.070$). Children had a lower rate of loss to follow-up compared with adults (13.1% vs. 36.6%, $P < 0.001$). Rate of clinical reflux, including symptomatic reflux and reflux esophagitis, was comparable between children and adults (26.5% vs. 29.6%, $P = 0.518$). However, children had a lower clinical failure rate than adults (4.4% vs. 12.3%, $P = 0.012$). Both mean post-POEM Eckardt score (0.7 vs. 1.5, $P < 0.001$) and median resting LES pressure (7.0 vs. 11.1 mmHg, $P = 0.001$) were lower in children than in adults. Kaplan–Meier analysis showed that the risk of clinical failure was lower for children than for adults (log-rank test, hazard ratio (HR) = 0.37, 95% confidence interval (CI) 0.15–0.91, $P = 0.023$, Fig. 1).

Differences between our previously published and current studies in patients of children

As shown in Supplemental Table 1, the 3 previous studies were performed in Zhongshan Hospital (26 cases, original article; 1 case, case report) and Children's Hospital, Fudan University (21 cases, original article) at 2015, 2015, and 2018. The mean follow-up time of the 3 studies was 24.6, 5.5, and 13.2 months, respectively. The mean procedure durations of the 3 studies were 39.4, not defined, and 40 min, respectively. Technical failure occurred in 3.7%, 0, and 0, and no mAEs occurred in the 3 studies.

Table 4 Clinical reflux and clinical response outcomes in children

Variables	Number
Clinical reflux evaluation	
Clinical reflux, total = 111	30 (27.0%)
Symptomatic reflux, total = 104	15 (14.4%)
Reflux esophagitis, total = 66	17 (25.8%)
Reflux esophagitis grade, total = 15 ^a	
Grade A	12 (80.0%)
Grade B–C	3 (20.0%)
Grade D	0
Clinical response evaluation	
Loss to follow-up, <i>n</i> (%)	17 (13.1%)
Follow-up time, median (range)	40 (4–88)
Clinical failure, total = 113	5 (4.4%)
1 year	2 (1.8%)
2 year	2 (1.8%)
3 year	4 (3.5%)
4 year	5 (4.4%)
5 year	5 (4.4%)
6 year	5 (4.4%)
Post-POEM Eckardt score, mean \pm SD	0.7 \pm 1.0
Post-POEM resting LES pressure, median (range), mmHg	7.0 (4.2–21.5)

POEM peroral endoscopic myotomy, SD standard deviation, LES lower esophageal sphincter

^aAmong 17 patients with esophagitis, 2 were not evaluated for grade

Table 5 Comparison of outcomes between children and adults

Variables	Adults	Children	<i>P</i>
Perioperative outcomes' evaluation			
Technical failure	15 (0.9%)	1 (0.8%)	1.000
Major adverse events	54 (3.1%)	5 (3.8%)	0.795
Clinical reflux evaluation			
Clinical reflux, total = 1,231	331 (29.6%)	30 (27.0%)	0.577
Symptomatic reflux, total = 1,212	219 (19.8%)	15 (14.4%)	0.187
Reflux esophagitis, total = 811	175 (23.5%)	17 (25.8%)	0.763
Clinical response evaluation			
Loss to follow-up, n (%)	641 (36.6%)	17 (13.1%)	< 0.001
Follow-up time, median (range)	45 (1–87)	40 (4–88)	0.070
Clinical failure, total = 1,221	136 (12.3%)	5 (4.4%)	0.012
Post-POEM Eckardt score, mean ± SD	1.5 ± 1.5	0.7 ± 1.0	< 0.001
Post-POEM resting LES pressure, median (range), mmHg	11.1 (1.1–42.9)	7.0 (4.2–21.5)	0.001

POEM, peroral endoscopic myotomy, *SD* standard deviation, *LES* lower esophageal sphincter

Postoperative clinical reflux rates of the 3 studies were 19.2%, 100%, and 28.6%, respectively. Clinical success rates of the 3 studies were all 100%. Compared with our 3 previous studies, the current study was multi-center, with much larger database (130 cases), longer follow-up time (median, 40 months), and shorter procedure duration (median, 30 min). The outcome evaluations were 0.8% of technical failure rate, 3.8% of mAEs, 27.0% of postoperative clinical reflux rate and 95.6% of clinical success rate.

Discussion

Owing to the low incidence of pediatric achalasia, the optimum management of achalasia in pediatric patients remains unclear. Previous studies of achalasia treatments failed to standardize a technical procedure and follow-up protocol. Traditional treatment methods for pediatric achalasia include medication, botulinum toxin injection,

and pneumatic balloon dilatation, which are associated with a high rate of clinical failure and serious complications [24–26]. Laparoscopic Heller myotomy is a surgical treatment for children that appear to provide better long-term efficacy. However, recent studies show that additional treatments are required in up to 25% of children during the follow-up period [27, 28]. As children have a long life expectancy, a safe and effective alternative treatment is needed to avoid long-term recurrence.

POEM is a novel endoscopic therapy for achalasia that is less invasive than conventional surgical myotomy. However, there are only preliminary reports of its safety and efficacy in children. In 2012, Maselli et al. reported the first pediatric case of POEM in a 3-year-old child who was asymptomatic and achieved a normal weight 1 year after the procedure [29]. In 2015, we successfully performed POEM in an 11-month-old patient with achalasia and severe malnutrition. Six months after the procedure, the child recovered well without regurgitation or persistent vomiting [13]. Another study from our team prospectively enrolled 26 children and reported no mAEs related to POEM. With a mean follow-up period of 24.6 months, no clinical failure occurred, and 5 patients (19.2%) developed clinical reflux [5]. The most recent study, by Miao et al., retrospectively reviewed 21 pediatric cases from 2014 to 2016. During a mean follow-up of 13.2 months, postoperative Eckardt score and LES resting pressure significantly decreased. All patients experienced significantly alleviated or resolved symptoms, and 6 patients had signs of clinical reflux [8].

Studies of POEM in adults have recently become more common, some of which even report outcomes from more than hundreds of patients [1, 20, 30]. In these studies,

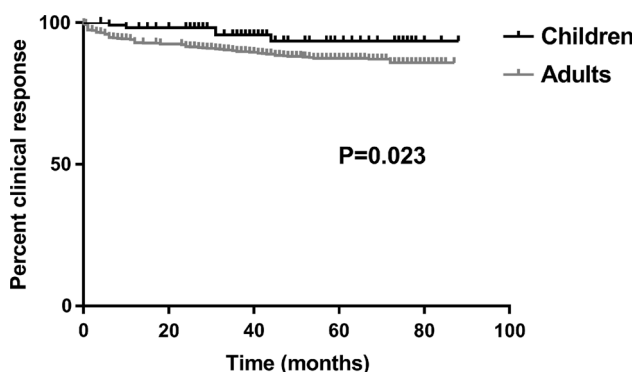


Fig. 1 Long-term clinical response of children and adults. Univariate log-rank test showed a lower risk of clinical failure in children than in adults (*HR* = 0.37, 95% *CI* 0.15–0.91, *P* = 0.023)

POEM shows promising advantages for the treatment of achalasia in adults, with low rates of adverse events and a high clinical response. However, all previous studies of POEM in children are small scale, involving not more than 30 pediatric patients [5, 8–12]. Thus, it is difficult to systematically evaluate and avoid statistical bias in these studies. Therefore, it is necessary to systematically explore the safety and efficacy of POEM in children using a more comprehensive and large database, and comparing its outcomes with those in adults. However, no previous studies have performed this comparison.

In our study, 130 patients, i.e., children undergoing POEM at three tertiary centers were analyzed and compared with 1749 adults. Clinical and procedural characteristics, perioperative outcome evaluation including technical failure and mAEs, and postoperative clinical reflux and clinical failure during follow-up were analyzed and compared. To our knowledge, this is the largest multi-center study with the largest database of POEM information worldwide, regardless of the age of patients. In addition, this is the first multi-center study of children with achalasia undergoing POEM. Therefore, our study provides a real-world analysis of the safety and efficacy of POEM for the treatment of achalasia in children.

We found that children had a shorter-disease duration, less sigmoid esophagus, and less prior treatment than adults, indicating an earlier and milder stage of achalasia in children. In addition, children had shorter lengths of esophageal tunneling and myotomy, a shorter procedure time, and a longer hospital stay than adults. The shorter procedure time might be related to the earlier stage of achalasia and shorter esophagus length in children than in adults. When we stratified children by age ranges (0–6, 7–12, and 13–17 years), we found that younger children had shorter lengths of esophageal tunneling and myotomy and a longer hospital stay. This longer hospital stay may be due to a greater level of attention from doctors.

Perioperative outcomes such as technical failure and mAEs indicate the safety of POEM, which should be a foremost consideration. In our study, the perioperative outcomes were acceptable in children patients. Only five children experienced mAEs, which were resolved by conservative treatment. Therefore, our findings demonstrate that POEM can be safely performed in children. In our previous study, we demonstrated that technical failure is mainly due to submucosal fibrosis, whereas mAEs are associated with doctor experience, air insufflation, and mucosal edema [17, 18]. In the present study, there were no significant differences in these factors between children and adults, which might explain their similar perioperative outcomes.

Postoperative clinical reflux is another critical concern regarding POEM, resulting from damage to the anti-reflux

structure. In our study, the postoperative clinical reflux rate was 26.5% in children, which was comparable to that in adults. Although a relatively high proportion of children developed reflux, all experienced relief by treatment with proton pump inhibitors without further invasive procedures. In addition, most only developed mild esophagitis (Grade A), and no severe esophagitis (Grade D) occurred. However, due to the relatively high rate of reflux and increased risks of Barrett's esophagus, stricture, and cancer in reflux patients, it is necessary for children to receive continuous follow-up evaluation throughout their lifetime [5].

Postoperative clinical response, an indicator of long-term efficacy, is extremely important in children owing to their long life expectancy. After its recurrence, rePOEM may require a longer procedure time, and its clinical response may be lower [31, 32]. In our study, only five children experienced clinical failure, of whom one had received prior treatment of dilation. All received rePOEM and experienced relief during follow-up. To avoid the influence of prior treatment on the efficacy of POEM, we recommend that children with achalasia receive POEM as the first choice to decrease its technical and clinical failure (0.8% and 4.4%, respectively). In our study, children had a lower rate of loss to follow-up compared with adults (13.1% vs. 36.6%), suggesting that children tend to complete follow-up better in the real world. Also, during a median follow-up of 40 months, children showed a significantly better clinical response than adults. This might be explained by the earlier and milder stage of achalasia in children than in adults (i.e., shorter disease duration, less sigmoid esophagus, less prior treatment). In addition, children tended to recover faster than adults after the procedure, such as nutrition condition and growth. This may also explain the greater improvement of postoperative symptoms in children than in adults.

Although our study created the largest multi-center database of long-term outcomes of POEM in children worldwide, some limitations were unavoidable. Owing to its retrospective design and relatively high rate of loss to follow-up, the results of our study could be influenced by potential selection bias, especially for long-term outcome evaluation. In this real-world Chinese setting, many patients from economically backward countries did not return for follow-up, and many changed their phone numbers during the follow-up. Although this real-world study does not provide ideally homogeneous data, it combines multiple sources and background settings and thus reflects a more realistic situation [33]. Using this real-world information, we also found that the follow-up rate was much higher for children than for adults. Since Zhongshan Hospital is a general hospital, mainly serving adult patients, the age of children of Zhongshan Hospital is older than the other two children's hospitals. In China, patients

with a very young age, especially infants, tend to receive treatment in children's hospital. In addition, due to the low incidence of achalasia in children, fewer children were included in the study compared with adults, which might have created statistical bias between groups. In the future, additional studies of children with achalasia undergoing POEM should be conducted to verify the present findings.

In conclusion, we systematically analyzed the largest multi-center database of long-term outcomes of POEM for the treatment of achalasia in children. Children with achalasia can be safely and effectively treated with POEM, with a better clinical response compared with adults. Therefore, POEM could be a promising treatment option for children with achalasia.

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Compliance with ethical standards

Conflict of interest None disclosed.

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