

In response to Editors:

Science Editor: Issues raised:

- (1) The authors need to provide an editable manuscript of Word format.
- (2) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.
- (3) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.
- (4) The authors need to provide the Biostatistics Review Certificate, and to add the page numbers in the STROBE form.

Response: Thank you very much for your kind suggestion and effort to process the paper. We provided the manuscript revision in word format for this submission. We added the PMID, DOI in all reference list and the “article highlight” as well. We also added the column of page numbers for each topic assessment in the STROBE form. Last, we have attached the Biostatistics Review Certificate from our statistician already. (We highlighted the revision context with red color)

Editorial Office Director: I have checked the comments written by the science editor.

Response: Thank you very much for your effort to process the paper.

Company Editor-in-Chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 12 words).

Response: Thank you very much for your thoughtful suggestion. We changed the title of the manuscript from “Detection of Gastroesophageal Reflux and Symptom Association in Children with Esophageal Atresia by Combined Video, Multichannel Intraluminal Impedance and pH Study” to “**Detection of reflux-symptom association in children with esophageal atresia by video-pH-impedance study**” (12 words) and changed the running title to “**Detection of reflux in children with EA by video-pH-impedance**”

In response to the Reviewer#1:

Reviewer #1: The present study is methodologically well conducted. The findings of the analysis using video MII-pH study are clear and correctly presented, comparison with histopathology is accurate. Video MII-pH study appears as an interesting technique even if at the moment evidences are not that solid, however authors clearly recognize this and suggest further investigation. On larger scale studies, being able to correlate GERD related symptoms with the MII-pH findings would help to validate this technique. Could you mention if surgery were performed open or laparoscopic? both for primary repair and delayed repair. Could you mention if patients underwent esophageal (anastomotic) dilatation due to strictures? or were dilatations maybe routinely performed in your hospital? It would be interesting to know if the two patients who underwent fundoplication reported different results from the rest.

Response: We would like to thank you very much for your positive and constructive comment in our pilot study. We answered to your questions as the following;

Could you mention if surgery were performed open or laparoscopic? both for primary repair and delayed repair. Could you mention if patients underwent esophageal (anastomotic) dilatation due to strictures? or were dilatations maybe routinely performed in your hospital?

All of our patients received open surgery both for primary and delayed repair. In our hospital, we performed esophageal dilatation according to patient's symptoms (dysphagia, vomiting, etc.) and signs (significant narrowing of anastomotic site from esophagogram or endoscopy), not routinely. Seven of them (47%) had significant esophageal stricture and underwent esophageal dilatations (1-7 times, bougie or balloon dilatations) without any serious complications. The outcome of esophageal stricture has been very good.

It would be interesting to know if the two patients who underwent fundoplication reported different results from the rest.

Thank you for your interest. There were 2 patients who underwent fundoplication in the present study.

The first case; she is 4.3 years old, EA type D with primary repair after birth. She had feeding intolerance, hypersecretion and hematemesis at 7 months of age. Endoscopy and MII-pH were investigated at that time and she was diagnosed with esophageal eosinophilia and GERD. EHF, 6-food elimination, PPIs and prokinetics were started but could not wean off. Re-endoscopy and MII-pH showed no GERD improvement with clinical hypersecretion/cough and vomiting, then she underwent fundoplication* 2 times. At the time of enrollment to the present study, she still had significant acid reflux with

cough-related reflux during monitoring and severe esophagitis from histopathology. We stepped up PPIs, added baclofen and gaviscon and plan to re-scope, biopsy and perform Video-MII-pH study again next year. Interestingly, mom reported that clinical symptoms of hypersecretion/ cough and vomiting were better with baclofen and gaviscon??

The second case; she is 11.9 years old, EA type C with primary repair after birth. She received first endoscopy and pH study at aged 2 years and diagnosed reflux esophagitis from endoscopic finding (LA class C), histopathology and pH study (RI 10.9%). Then PPIs was started at that time. After follow-up endoscopy and pH study → not improve then she underwent fundoplication* 2 times at age 5 and 11 years old. At the time of enrollment to the present study, she had normal acid reflux and only one symptom of dysphagia during monitoring without dysphagia-related reflux. However, there was LA classification B from endoscopy and severe esophagitis from histopathology.

In summary, these 2 cases had severe GERD that not response well to the optimal medications, however, the outcome of fundoplication was still unsatisfied.

Reviewer #2: Overall the study addresses an important health care issue in children underwent EA repair. Although the study number is very limited the contents could add to the existing literature. Abstract addresses most of the components of the study. Please expand the abbreviations when it is used for the first time. Introduction: addresses the existing literature and the aims of the study. Methods are alright. In the inclusion, it is not understood why the children up to 18 years are included. The authors should have studied all cases at least within one year of surgery for EA and at certain interval thereafter. The cases with fundoplication should have been avoided. Results are reasonable. Mention the lowest and the highest age of the study population. Discussion is reasonable. The limitations addressed. Please discuss how early MII-pH study could be done after EA repair. How often such studies should be repeated to optimize medical therapy so that Barrett's esophagus could be avoided.

Response: We would like to thank you very much for your helpful and thoughtful suggestion. We revised our manuscript according to your suggestion as following;

Abstract - Please expand the abbreviations when it is used for the first time.

We added “combined video with multichannel intraluminal impedance and pH” in front of it's abbreviation “MII-pH” study (page 3)

We added the European Paediatric Impedance Group instead of “EURO-PIC”

(page 3)

Furthermore, we also expand the abbreviations of other words as following;

Introduction section - We added “the European Society of Paediatric Gastroenterology Hepatology and Nutrition and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition” in front of it’s abbreviation “ESPGHAN-NASPGHAN” (page 5)

Materials and metods section - We added “the British Society of Paediatric Gastroenterology, Hepatology and Nutrition” in front of it’s abbreviation “BSPGHAN” (page 6)

Methods - Methods are alright. In the inclusion, it is not understood why the children up to 18 years are included.

We omitted the word “(age <18 years)” from “children (age< 18 years) diagnosed with EA” and replaced with “children diagnosed with EA” instead. (page 5)

The authors should have studied all cases at least within one year of surgery for EA and at certain interval thereafter.

Thank you very much for your thoughtful suggestion. We accept this limitation of our cross-sectional study.

In the past, we investigated children diagnosed EA according to symptoms and signs during follow-up. For example, endoscopy with dilatation if there was clinical suspected esophageal stricture and pH or MII-pH study if there was clinical suspected GERD. However, after ESPGHAN-NASPGHAN launched the clinical guideline for EA patients in 2016, we managed patients following the guideline and conduct the researches involved including this study in the meantime. We plan to collect the video-MII-pH study in infant diagnosed EA after surgical correction and during follow-up as well, however, it will take time for that results.

The cases with fundoplication should have been avoided.

Thank you for your comment. The limitation of our pilot study is the small number and in homogenous participants that we also mentioned in the discussion part (page 13). However, we tried to analyze the data again by exclude the 2 cases with fundoplication and the statistical outcomes were not different from the previous results (please see the attached table). As a result, we think it should be good if we could maintain 15 participants for the data analysis in our study.

Table 2. Patient demographic data and characteristics (n = 15)

Characteristics	Median (IQR) or n (%)	Reanalysis (n=13)
Male sex	6 (40)	6 (46.2)
Age (years)	3.1 (2.2-9.8)	3.3 (1.8-10.2)
Weight for height (%)	100 (89.4-104.6)	100 (89.4-104.6)
Previous symptoms		
General		
- Discomfort/ Irritability in infants	3	2
- Failure to thrive or weight loss	8	7
- Feeding refusal	3	3
Total	10 (66.7)	9 (69.2)
Gastrointestinal		
- Recurrent regurgitation with or without vomiting	9	8
- Heartburn or chest pain	1	1
- Epigastric pain	1	0
- Hematemesis	1	0
- Dysphagia, odynophagia	6	6
Total	11 (73.3)	10 (76.9)
Airway		
- Wheezing, stridor	4	4
- Cough	9	8
- Hoarseness	2	2
Total	10 (66.7)	9 (69.2)
Previous signs		
General		
- Dental erosion	4	2
- Anemia	2	2
Total	4 (26.7)	2 (15.4)
Gastrointestinal		

- Esophagitis	8	7
- Esophageal stricture	7	6
- Barret's esophagus	2	1
Total	12 (80)	11 (84.6)
Airway		
- Asthma	1	1
- Recurrent respiratory tract infection	8	6
- Recurrent otitis media	2	2
Total	8 (53.3)	6 (46.1)

Table 3. Esophagogastroduodenoscopy findings and biopsy results of children with EA after esophageal anastomosis (n=17)

Classification	N (%)	Reanalysis (n=15)
Los Angeles Classification		
Normal	8 (47.1)	8 (53.3)
A*	2 (11.8)	2 (13.3)
B**	4 (23.5)	2 (13.3)
C***	3 (17.6)	3 (20)
Pathology		
Normal	6 (35.3)	6 (40)
Mild esophagitis	2 (11.8)	1 (6.7)
Severe esophagitis	9 (52.9)	8 (53.3)

Table 4. Parameters used and the analysis result of combined MII-pH study in children diagnosed EA after esophageal anastomosis (n=17)

Parameters	Median (IQR)	Reanalysis (n=15)
Monitoring period excluding fed periods (hours)	21.2 (19.3-22.1)	21.0 (19.1-22.1)
RI (%)	2.7 (0.5-9.5)	2.7 (0.5-9.5)
Longest reflux period (minutes)	20 (5-29)	15.85 (4.05-26)
Esophageal clearance (minutes)	1.4 (0.6-2.5)	1.4 (0.6-3.1)
Total reflux (times)	19 (11-36)	19 (11-36)
- Acid	9 (4-14)	9 (4-14)
- Weakly acid	10 (6-15)	10 (6-15)
- Weakly alkaline	0 (0-0)	0 (0-0)
Mean bolus clearance time (seconds)	14.9 (10.4-19.2)	14.9 (10.4-21.7)

Table 5. Parameters used and results from the analysis of combined video MII-pH study in children diagnosed EA after esophageal anastomosis between using and non-using acid suppression therapy (n=17)

Parameters	Acid suppression therapy (n = 7)	Re-analysis (n = 5)	No acid suppression therapy (n = 10)	P-value
Monitoring period (hrs)	21.2 (18.1-24.5)	19.1 (17.8-22.9)	21.3 (19.5-22.1)	0.696
RI (%)	7.1 (1.4-10)	7.1 (2.8-9.8)	1.45 (0.3-4.2)	0.240
Longest reflux period (mins)	29 (5-96)	23.3 (13-34.9)	16 (4-24)	0.143
Esophageal clearance (mins)	2.0 (1.0-3.6)	2 (1.3-3.9)	1.0 (0.5-1.7)	0.261
Total reflux (times)	19.0 (11-46)	19 (15-41)	19.0 (11-29)	0.660
- Acid	10.0 (4-16)	10 (6.5-18.5)	6.5 (3-11)	0.558
- Weakly acid	13.0 (4-32)	13 (5.5-23.5)	9.0 (6-14)	0.733
- Weakly alkaline	0.0 (0-0)	0.0 (0-0)	0.0 (0-1)	0.123
Mean bolus clearance time (secs)	11.9 (9.3-16.5)	11.9 (10.2-18.5)	17.3 (10.4-21.7)	0.242
Number of symptoms (times)	3.0 (1.0-5.0)	3.0 (1.0-6.0)	4.0 (1.0-7.0)	0.452
SI (%)	25 (0.0-50)	25 (0-60)	10.5 (0-66.7)	0.840
SSI (%)	1.4 (0-5.3)	2.8 (1.4 (0-5.3)	3.7 (0.0-17.6)	0.419
SAP (%)	73.9 (0-90.9)	73 (0-95.5)	83.9 (0-99.1)	0.649

Table 6. Symptoms and symptom correlation from video recording in children with EA (n=~~17~~ 15)

Symptom	Symptoms	Symptom-reflux	Acid	Weakly acid	Non acid	SI	SSI	SAP
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correlation								
Cough	35-31	16 (45.7%) 14 (40%)	9	7-5	0	58.5 (6.2-100)	2.9 (0.3-7.1)	95 (18.9-99.2)
Vomit	9	8 (89%)	5	3	0	75 (50-100)	3.9 (2.3-60.7)	99.6 (87.8-99.9)
Irritability or unexplaine d crying	7	5 (71%)	4	1	0	50 (25-50)	3.8 (2.5-3.8)	92.8 (72.9-92.8)
Dysphagia	1	0 (0)	0	0	0	0	0	0
Total	52	29 (55.7%)	18	11	0	58.4(27-100)	3.9(1.3-7.1)	92.3 (77.4-99.6)

Results - Results are reasonable. Mention the lowest and the highest age of the study population.

We changed from there were 15 patients diagnosed with EA recruited into the present study. The median age was 3.08 (2.17, 9.83) years to “**The median age was 3.08 (range from 1.4 to 12.9) years**” (page 9)

Discussion - Please discuss how early MII-pH study could be done after EA repair. How often such studies should be repeated to optimize medical therapy so that Barrett’s esophagus could be avoided.

Thank you very much for your helpful suggestion. We added “**As the prevalence of GERD and it’s complications tended to increase very early, the ESPGHAN-NASPGHAN guidelines for children with EA recommended using PPIs in all EA patients in the neonatal period and should be longer, depending on persistence of GERD. As a result all EA patients should undergo MII-pH study, at least, at the time of discontinuation of PPIs and during long-term follow-up.**”

Moreover, we stressed that “**not only MII-pH study but also EGD and esophageal biopsy to optimize therapy so that Barrett esophagus and esophageal carcinoma, hopefully, could be avoided**” in the discussion part as well. (page 12)

Reviewer #3: it is a good study

Response: Thank you very much for your very positive to our manuscript. We tried to design the research study as best as possible to extend the new knowledge that be benefit the current clinical practice.

Other revision:

- We would like to add our funding as the following;

ACKNOWLEDGEMENTS

The author would like to thank Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University (Grant No RA62/001), the Pediatric Gastroenterology and Hepatology STAR (Special Task Force for Activating Research), Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University for research funding. (page 15)

Tanisa has another affiliation that we would like to add in: **Center of Excellence in Neurogastroenterology and Motility** (page 2)

Table and figure legend:

Change N to “n”