Dear editors,

Thank you for considering our manuscript, please find enclosed our point by point response to the reviewers comment.

Thank you
Mohamed Mutalib

Reviewer #1:

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Rejection

**Specific Comments to Authors:** I appreciate the authors effort in accumulating the current data surrounding the use of EndoFLIP in investigating GI motility disorders particularly in the paediatric population. However, to be fair the manuscript offers little addition to what is already known about this modality. Limited data has been presented in regards to its utility in the paediatric population which supposedly was the main theme of this review. The modality as of now, only has a modest advantage over the conventional manometry which continues to be the mainstream when it comes to diagnosing GI motility disorders.

EndoFLIP is an emerging technology that offers a complementary diagnostic tool to the existing GI motility investigations. The data is rapidly emerging in the adult population and we agree, there are limited studies in paediatrics. As we explained in the manuscript, both conventional and high-resolution manometry remain the gold standard diagnostic modalities for many GI motility disorders. However, they do suffer from many limitations and EndoFLIP appear to complement some of their shortcoming. The aim of this review was to raise awareness and present a structure on the available literature focusing on paediatric practice. The field of paediatric GI motility often lags behind adult practice and it took a considerable time to establish the existing diagnostic tools in paediatric including but not limited to manometries, pH and pH impedances. The available data, both in paediatric and adult, does not support, neither did we claim, that EndoFLIP can replace existing GI motility investigation, rather it offers an add on value and it can provide a base to build upon.
The overall quality of English language is suboptimal with numerous grammatical errors which need to be fixed.
We went through the manuscript and corrected the spelling and grammar. We will be grateful if you can provide specific examples we may have missed.

The authors could have provided a more integrative review instead sharing based on their experience, how this modality could preferentially be utilized in certain subset of patients instead of the conventional tools.

At present, with the currently available data, EndoFLIP is not recommended to be used in place of any existing motility investigation. We explained in the article the available evidence (and stated when this evidence is weak) to guide the readers on the utility of EndoFLIP for particular GI disorders. In some disorders such as EoE and pylorus instability, EndoFLIP provides a new set of data that can guide clinical management and identify a subset of patients who may require a different clinical pathway. While on other disorders such as achalasia, the data is still emerging.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: 1. This is a narrative review on the use of an impedance planimetry with endoscopic functional lumen imaging probe (EndoFLIP) as a device to investigate gastrointestinal motility disorders with a special focus on paediatric practice. My overall impression is that this a biased review. First, the authors do not provide the methodology how they collected the relevant studies for their review.
We have added the search method after the aim at the end of the introduction.

Second, the authors do not critically analyse the studies and all positive findings are taken as absolute truth.
EndoFLIP is an emerging technology and its use is actively explored with data continuously presented. We presented the summary of the findings and the studies in relation to both children and adults. We also stated in the limitation of evidence in all areas. In addition, we reported on the limitations of the most published data on EndoFLIP. The aim was to give the reader an overall view on the use of EndoFLIP with focus on strength and limitation of evidence in each of the known GI disorders where EndoFLIP can be used.

2. The Abstract is written poorly. It is just a condensation of the Introduction. It contains nothing about how the review was conducted (methodology), the main findings from the review (results), and a concluding remark about the current and future use of the new device (conclusion). We followed WJCP guidance on abstracts for review articles which suggests a non-structured abstract. Considering this was not a systematic review and the data was presented according to specific disorder, it will be challenging to pool the results or have an overall conclusion. We did however, restructured the abstract and added a concluding paragraph.

3. In the Introduction, the authors explain the principles of EndoFLIP and how it is applied in clinical practice. However, they have not clearly mentioned that the device is used during endoscopy and thus under sedation and/or anaesthesia. Are there any potential effects from the anaesthetic agents that may affect the interpretation of the findings from EndoFLIP?

Thank you, that was an oversight. We have added a statement to explain EndoFLIP is used during endoscopy. We have already stated that the effect on anaesthesia on EndoFLIP findings is unknown and it yet to be studied but as all FLIP studies (both in children and adults) are done under anaesthesia, the effect should be uniform.

Also, are normative data from healthy individuals required before the measurements obtained from EndoFLIP can be interpreted? If yes, this is clearly a major hurdle to extending the use of the device from adult practice to paediatric practice.

Thank you for raising this important area. Correct, the available adult data are mostly from healthy volunteers and extrapolating them into paediatric can present a
limitation but this dilemma is widely present in paediatric GI motility due to challenges of obtaining ethical approval for these investigations in healthy children. The data from other motility investigations such as pH impedance, and all types of manometries were collected either by proxy or from children with non-GI disorders who may require anaesthesia or other investigations. We aim to raise the awareness about the emerging technology and enrich the discussion about the acute need of normative paediatric data.

4. The review actually focuses on the following conditions: achalasia, eosinophilic oesophagitis, gastrooesophageal reflux disease, oesophageal atresia and oesophageal strictures, pyloric disorders, and anal sphincter disorders. However, according to systemic review by Desprez et al. (Reference 19), there are only reasonably sufficient studies to comment on the use of EndoFLIP on achalasia. As for the other disorders, the published studies are either too small in size or the methodology was not sufficient clear for comment.

This is correct, and we believe we have presented a balanced review of the available evidence. It is also true that most of the published studies are either small in sample of not sufficiently powered for grade A evidence, but EndoFLIP is an emerging technology which showed a promising add on value in investigation certain GI conditions. We aim to present an overall review to guide the reader on the available evidence and to show the strength and limitation of EndoFLIP.

It is also obvious in this manuscript that the authors have skipped the critical analysis on their cited studies and presented each and every one as if they are absolutely true. Presentation like this is not acceptable. This statement was answered in the second point above.

5. When discussing each category of diseases, the authors should clearly state which data and studies refer to adults and which ones are for children.

Clarified

6. In the Conclusion, the authors have painted a very optimistic view on the use of EndoFLIP in paediatric practice. However, a critical look at the presentation can only support its use in a subset of children with achalasia when conventional high-resolution manometry fails to secure a diagnosis. The current evidence does not support the use of EndoFLIP in children who have pyloric and anal sphincteric
disorders, while its use in other gastrointestinal motility disorders should be treated as experimental until further evidence, especially those from comparative studies is available.

We stated in the conclusion that EndoFLIP can add a complementary data to the standard motility investigations which is supported by the current published data. We have added a statement to clarify that EndoFLIP should not be used to replace the standard diagnostic investigations. The available or lack of published literature on a specific disorder is summarised in the main article.

7. About the References, the authors should explain how they are collected from the literature. It is important that the authors approach the literature search systematically so that all relevant studies are captured including studies showing negative findings.

we have added a paragraph in the introduction to detail the search methodology.

8. Figure 1 can be deleted.

Deleted

9. In Figure 2, the authors should explain with indicators the different components of the device.

Added

10. In Figures 3 to 7, the authors should explain how the findings are relevant to the diagnosis or the results of the intervention.

Explained in the text

Reviewer #1: 1. Thank you for responding to my previous comments and re-submitting the manuscript. The changes have allowed me to look at the paper in a more structured manner.

2. The authors stated that their purpose was to review the uses of EndoFLIP as a tool to investigate gastrointestinal motility disorders with a special focus on paediatric practice. This is NOT valid. They actually reviewed all possible clinical applications of EndoFLIP and tried to sell it to paediatric practice, even in the absence of evidence.

I am afraid we are not trying to “sell it”. This review looked at an overview of evidence on the use of EndoFLIP with a special focus on paediatric practice, all evidence was reviewed and the paediatric evidence were laid out. This will allow WJCP to have a
clear view on what is available and the strength and limitation of the available literature.

3. The authors provided how they had searched the literature for relevant publications. They searched pubmed database for English Language literature on the following keywords: EndoFLIP; Gastrointestinal Disorders; GI disorders; oesophagus; pylorus; rectum; anorectum; paediatric; children using AND/OR combination as appropriate. I followed the search strings [endoflip AND (pediatric OR children) AND (gastrointestinal disorder OR esophagus OR pylorus OR rectum OR anorectum)] and obtained 18 publications. However, in their review, the authors only quoted 9 articles relevant to paediatric practice. This number is smaller than the articles I have found. The authors must have their own selection and exclusion criteria but they did not disclose in their manuscript.

As we stated in our previous response to the reviewer and the aim of this manuscript. This is not a systematic review and we did not aim to pool the results of all published studies.

The reviewer is correct, if they used the set search criteria in pubmed, they will obtain 18 items, if they sort by journal they will understand why we have included only set articles in our manuscript:

Item 2. Was published in August 2023 after our manuscript was written and they focused on EsoFLIP usage. Their results are in line with what we stated in the manuscript.

Item 3 and 5 are reporting on the safety of using EndoFLIP

Item 6 is a letter to editor

Items 11 and 12 are similar and both reported on safety of the use of EndoFLIP

Item 13 is a case report of a duplication cyst

Item 14 is not a paediatric paper

Item 18 looked at a novel diagnostic tool in EoE and EndoFLIP is used a marker for distensibility.

4. In presenting the relevant studies, the authors failed to explain clearly the patient population and the demographic data. Important information such as the sample
size and mean age or age range of the studied subjects is distinctively absent. Associated morbidities, such as neurodevelopmental disorders, other than the gastrointestinal disorders are not mentioned. Without this background information, the readers can be easily misled to believe that EndoFLIP has been widely used in children from birth to adolescence (which is not true).

We respectively disagree with the reviewer on this point. This is a simple review to give the readers of WJCP an overview on EndoFLIP usage with the aim of reviewing the literature and summarising paediatric practice. This is not a systematic review and we never aimed to pool the results or compare methodological difference. We, nevertheless, have highlighted the limitation of the literature particularly in paediatric due to small case series and/or small sample size. All paediatric studies are very small and attempts to compare or pool the data will likely to result in skewed outcome.

EndoFLIP has been increase used in paediatric practice. The FDA has approved EndoFLIP use in children > 5 years of age and it has been used in children < 5 years of age, the reviewer would have seen that the team from John Hopkins led by Hoskins et al have published their experience in the use of EndoFLIP in children < 5 years of age

5. For achalasia, the authors found two studies. Reference 33 is a retrospective study on 10 children of mean age 13.3 ± 3.3 years. Reference 34 is a case report about an 11-year-old child.

The outcome has been similar to adult studies.

6. For eosinophilic oesophagitis, the authors found three studies. Reference 44 involved 59 subjects aged from 9 to 21 years. Reference 45 involved subjects aged from 3 to 18 years, comparing 88 children with eosinophilic esophagitis to 44 children without the condition. Reference 46 is a study with 25 adults.

7. For gastro-oesophageal reflux disease, the authors did not find any relevant study.

8. For oesophageal atresia, the authors found one study. There were 9 subjects aged 9 to 21 years.

9. For oesophageal stenosis, the authors found one study. There were 18 children with a median age of 13.7 years and the youngest was 10 months old.

10. For pyloric disorders, the authors found two studies. Reference 62 involved 59 subjects but only 23 who were older than 10 years underwent EndoFLIP. Reference 63 involved 12 subjects of mean age 10.7 ± 4.2 years. Therefore, there were a total of
22 children who had undergone EndoFLIP for pyloric disorders in the literature in non-comparative studies. 11. For disorders of anal sphincter, the authors did not find any relevant study. 12. Going through all these nine studies, I disagree with the authors conclusions. I can only conclude that EndoFLIP is at most a procedure that is under exploration for use in paediatrics. The procedure is feasible in older children (over the age of 10 years). The impact of EndoFLIP on patient outcomes is largely unclear, when comparative studies are almost unavailable.

Points 6-11 are stating the outcomes of the included studies and do not raise specific queries to answer.

Point 12: I am afraid we have to, respectively, disagree with the reviewer here! EndoFLIP is not experimental and as we stated in the points above, FDA has approved EndoFLIP use in children > 5 years of age and many studies have reported on the use of EndoFLIP. The reviewer has reached an unsupported conclusion by stating EndoFLIP is only feasible in children > 10 years of age.

The point of lack of comparative studies is valid, but this is true in almost all paediatric studies. We responded to a similar point in our first response to the initial submission. The data in most paediatric GI motility investigations are not compared to healthy individuals due to ethical constrains in performing invasive investigations in healthy children. We hope this will change and we are aware of many researchers who are working with ethical review boards to address this issue. We believe this will be for the good of paediatric practice. In the meantime, this article alongside others will aim to highlight the struggle of limited research in paediatric and we hope to stimulate researcher from across the globe to address this issue.

13. The authors also fail to elaborate on the technical aspects if children are to undergo EndoFLIP with endoscopy. Age selection with respect to the actual size of the device has not been mentioned. Given that EndoFLIP comes with two sizes or lengths, the authors fail to explain how these different sizes are to be used. The authors also fail to explain the use of sedation and/or general anaesthesia when children have to go for EndoFLIP – what are the sedative or anaesthetic agents preferred, and which are to be avoided? Should muscle relaxants be used during the procedure?
I am not sure what does the reviewer mean by the technical aspects of EndoFLIP with endoscopy, we believe we have explained in details how EndoFLIP is performed.

At present and from the available literature, all studies are small studies and mostly reported on retrospective review of practice hence age and size selection are not strictly determined.

EndoFLIP catheters are two sizes, as we explained in the manuscript, the 16 size is used with EndoFLIP topography to study oesophageal body contraction while the 8 is used for other indications!

Reviewer #2: The authors have satisfactorily answered most of the concerns raised during the prior review. I have no further comments.