

## Research Article

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# A bibliometric analysis of peroral endoscopic myotomy for achalasia: Where have we been and where should we go next?

Han Zhang<sup>1\*</sup>; Fang Cheng<sup>1</sup>; Huang Zhong<sup>1</sup>; Wei Wei<sup>1</sup>; Zhong Huang<sup>1</sup>; Yan Peng<sup>2</sup>; Xiaowei Tang<sup>2</sup>

<sup>1</sup>Department of Gastroenterology, Zigong First People's Hospital, Zigong, China.

<sup>2</sup>Department of Gastroenterology, The Affiliated Hospital of Southwest Medical University, Luzhou, China.

### \*Corresponding Author: Han Zhang

Department of Gastroenterology, Zigong First People's Hospital, 42 Shangyihao Road, Zigong, 643000, Sichuan Province, China.

Email: 443191590@qq.com

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**Abbreviations:** Endoflip: Endoscopic Functional Luminal Impedance Planimetry; GERD: Gastroesophageal Reflux Disease; LHM: Laparoscopic Heller Myotomy; PD: Pneumatic Dilatation; POEM: Peroral Endoscopic Myotomy; WOSCC: Web of Science Core Collection.

## Introduction

Achalasia is an esophageal motility disorder, often manifested by dysphagia, regurgitation, chest pain, and weight loss, seriously affecting the quality of life [1]. In addition, achalasia has been reported to be associated with esophageal cancer [2].

## Abstract

**Background:** Peroral endoscopic myotomy (POEM), a treatment for achalasia, has experienced more than ten years of development with significant global progress. We conducted a bibliometrics analysis to reveal the publication trend, influential representative and their cooperation, knowledge base, and research hotspots in this field.

**Methods:** A pre-made search strategy was used to retrieve records related to POEM and achalasia in the Web of Science Core Collection database. VOSviewer, CiteSpace, Tableau Public, Origin-Pro software, and Online Bibliometric Analysis platform were employed for data analysis and visualization.

**Results:** 935 studies involving 711 original articles and 224 reviews were included. The number of publications and citations grew gradually between 2010 and 2020, peaking in 2020 and slightly reducing between 2020 and 2022. The USA, China, and Japan contributed the most significant publications. Showa University and Northwestern University were the top two prolific institutions. The author who published the most articles was Inoue Haruhiro from Showa University in Japan. *Surgical Endoscopy* published the most articles, while *Endoscopy* owned the most citations per paper. The keywords "Heller myotomy," "pneumatic dilatation," and "gastroesophageal reflux disease" ranked in the top five with 83,70, and 60 times, respectively.

**Conclusion:** POEM has come a long way in the last thirteen years, but there is still a long way to go. Comparison between POEM and laparoscopic Heller myotomy or pneumatic dilation, particular achalasia patients and other esophageal motility disorders, systematic review and meta-analysis, endoscopic functional luminal impedance planimetry application, and third space endoscopy were research hotspots and future direction.

Therefore, effective and safe treatment for achalasia patients is of paramount importance. Traditional first-line treatment modalities included pneumatic dilation (PD) and laparoscopic Heller myotomy (LHM) [3]. However, the high incidence of perforation complications and the high need for repeated dilation of PD have been criticized [4]. Besides, the invasive nature, slow

recovery, and high cost of LHM also limited its application in some special populations [4]. At this time, peroral endoscopic myotomy (POEM), which combined the minimally invasive nature of PD and the effectiveness of a single intervention of LHM, came into being in Japan [5]. Since the implementation of POEM by Inoue et al. in 2008 [5], POEM has experienced more than ten years of development with significant global progress. It has become the current first-line treatment for achalasia [6]. Many studies on POEM treatment for achalasia patients have been reported during this period. However, up to now, there has been no comprehensive and objective bibliometric visualization analysis on POEM in treating achalasia, except for two articles that analyzed achalasia [7] and POEM [8], respectively.

Bibliometric analysis, introduced by Alan Pritchard in 1969 [9], is a scientific quantitative analysis method of published studies that integrates philology, mathematics, and statistics. It focuses on the distribution structure, quantity relationship, and change law of literature information, providing a definite overview of the research field and revealing the development trend of the discipline. Many platforms, including VOSviewer, CiteSpace, and Bibliometric.com, can visually analyze literature based on years, countries, institutions, authors, journals, co-citations, and keywords in a given research field. So far, many bibliometric analyses have been published in various fields [10-12], including digestion and endoscopy [13-15]. Those studies summarized the research status of related subjects and provided the hot spots and future research direction, significantly promoting this field's development.

With the help of bibliometrics, this study analyzed relevant studies on the POEM treatment of achalasia. We aimed to reveal the publication trend, influential country, institution, author, and journal and their cooperation, knowledge base, and research hotspots in this field.

## Materials and methods

### Data collection

We used the following search strategy to retrieve records related to POEM and achalasia in the Web of Science Core Collection (WoSCC) database: TS=(achalasia) AND (TS=(Peroral endoscopic myotomy) OR TS=(Peroral endoscopic myotomy) OR TS=(Peroral endoscopic myotomy)). Document type was limited to original articles and reviews, and language was restricted to English. We retrieved articles, and exported full records and cited references to plain text files on July 20, 2023. Because the data came from the public database, the Institutional Review Board approval and written consent were not needed for our research.

### Data analysis

In this study, VOSviewer (version 1.6.19), CiteSpace (version 6.1.R6), Tableau Public 2021.3, and OriginPro 2022 software and Online bibliometric analysis platform (<https://bibliometric.com/>) were employed for data analysis and visualization. OriginPro software was used for the quantitative analysis of publications. Tableau Public software produced a global map showing the number of publications by country. The Online bibliometric analysis platform created a collaborative network map between countries. VOSviewer software was used for source and co-cited journal analysis, co-cited references analysis, and keyword

co-occurrence analysis. CiteSpace was used to carry out country cooperation analysis, institutional cooperation analysis, author cooperation analysis, and map the dual-map overlay of journals. Besides, CiteSpace was also used in keyword citation burst analysis. In the map generated by VOSviewer and CiteSpace, nodes represent items such as countries, institutions, authors, journals, references, and keywords. The size of the nodes represents the number of these items. The line thickness between nodes reflects the degree of collaboration or co-citation. The color of the nodes in VOSviewer represents the classification of these items, and the color of the nodes in CiteSpace reflects the time variation. Purple-rimmed circles in CiteSpace refer to the nodes with high centrality, highlighting the significance of these nodes in the network. The journal quartile and impact factor were derived from Journal Citation Reports 2022. The dual-map overlay of journals presents the relationship between journals and cited journals. References and keywords with citation bursts were those that had been cited significantly more frequently over a period.

## Results

### Publication and citation trends

As shown in Figure 1, we finally included 935 studies involving 711 original articles (76.04%) and 224 review articles (23.96%). The dynamic change in annual publication and citation numbers is presented in Figure 2. The number of publications grew gradually between 2010 and 2020, peaking in 2020 with 143 studies. However, there was a slight downward between 2020 and 2022, which was still higher than between 2010 and 2019. Similarly, citations increased steadily from eight in 2010 to 1070 in 2015 and then skyrocketed to 3199 in 2020. From 2020 to 2022, the number of citations decreased slightly, remaining three thousand times.

### Country/region analysis

A total of 50 countries worldwide were committed to studying POEM for achalasia. The top ten countries with the most publications are displayed in Figure 3A. Most countries in Eastern Europe, Western Asia, and Africa still had a research gap in this field (Figure 3B). Researchers from the USA in North America contributed the most significant number of publications and had the highest H-index (382 articles, 49) in this field. From Asia, China (182 articles, 35) and Japan (131 articles, 35) ranked second and third, respectively. These three countries account for half of the global publications (49.9%). Interestingly, Germany, the country with the lowest number of publications among the ten countries, had the highest average citations (62.74 per paper), followed by Canada (45.03). Figure 3C depicts the cooperation map, suggesting the close partnership among the various countries and regions. Notably, the USA had close ties with Italy, France, and Japan. With high centrality, Italy, England, the USA, Australia, and Belgium have cooperated with many countries and regions (Figure 3D). Interestingly, China ranked second in the total amount of publications but at the bottom in the centrality.

### Institution analysis

More than one thousand institutions worldwide were engaged in the study of POEM in treating achalasia. Among them, the top ten by the number of publications were Showa Univer-

sity (69), Northwestern University (44), Asian Institute of Gastroenterology (37), Fudan University (33), University of Chicago (25), Kobe University Hospital (22), Johns Hopkins Medical Institution (21), Niigata University (20), Fukuoka University (20), and Oregon Clinic (20) (Figure 4A). In the top 10 institutions, Japan and the USA each had four organizations, while India and China each had one organization. Notably, European institutions did not appear in the top ten list. Figure 4B displays the close cooperation among the various institutions. Regarding institutional partnerships, the Chinese University of Hong Kong in China had the closest links with global institutions. However, as the most prolific Chinese institution, Fudan University was mostly limited to domestic collaborations, such as with the Chinese People's Liberation Army General Hospital and Central South University. In addition, the top two institutions, Showa University and Northwestern University, also ranked third and second in the degree of cooperation, respectively. University of California San Diego, Tohoku University, and Oita University were newly active institutions in recent years.

### Author analysis

More than three thousand authors have conducted studies on POEM in treating achalasia. Among them, the top ten by the number of publications were Inoue Haruhiro (72), Khashab Mouen A (41), Nabi Zaheer (31), Pandolfino John E (29), Onimaru Manabu (26), Ramchandani Mohan (24), Patti Marco G (22), Sato Hiroki (22), Li Quan-Lin (20), and Hungness, Eric S (20) (Figure 5A). The author who published the most articles was Inoue Haruhiro from Showa University in Japan. Of the top ten authors, four were from the USA, three were from Japan, two were from India, and one was from China. Figure 5B presents the close cooperation among the various authors. Regarding collaboration between authors, Inoue Haruhiro and Khashab Mouen A, the two most prolific authors, also worked closely with authors worldwide. Interestingly, Chinese authors often cooperated with each other and lacked communication with foreign authors. Abe Hirofumi and Carlson Dustin A were active authors that had emerged in recent years.

### Journal analysis

Literature on POEM in treating achalasia has been published in 210 journals. The top ten journals with the most publications are depicted in Figure 6 and Table 1. The number of articles published by the top ten journals accounted for about 40 percent. *Surgical Endoscopy* (114 articles, 29), *Gastrointestinal Endoscopy* (54 articles, 25), and *Endoscopy* (34 articles, 18) ranked first, second, and third respectively, in the total number of articles and H-index. Besides, *Endoscopy* (68.3 per paper) was the journal with the most average citations. The second and third place in average citations per paper were *Journal of Gastrointestinal Surgery* (37.1) and *Gastrointestinal Endoscopy* (36.7), respectively. Of the top ten journals, six belong to the USA, two to Germany, one to England, and one to Japan. There are three journals with an impact factor greater than five, including *Endoscopy* (IF=9.3), *Gastrointestinal Endoscopy* (IF=7.7), and *Digestive Endoscopy* (IF=5.3). Figure 7A and Figure 7B show the density maps of journal analysis and journal co-citation analysis, respectively.

In the co-citation analysis, the co-cited journals were divided into the following three categories: green mainly represents professional journals in the field of gastroenterology or

comprehensive medical journals, such as *American Journal Of Gastroenterology*, *Gastroenterology* and *New England Journal of Medicine*, red represents academic journals in the field of digestive endoscopy, and blue represents academic journals in the field of surgery. As shown in Figure 7C, one main path was identified, indicating that articles published in "Health, Nursing, Medicine" journals were generally cited in those articles published in "Medicine, medical, Clinical" journals.

### References analysis

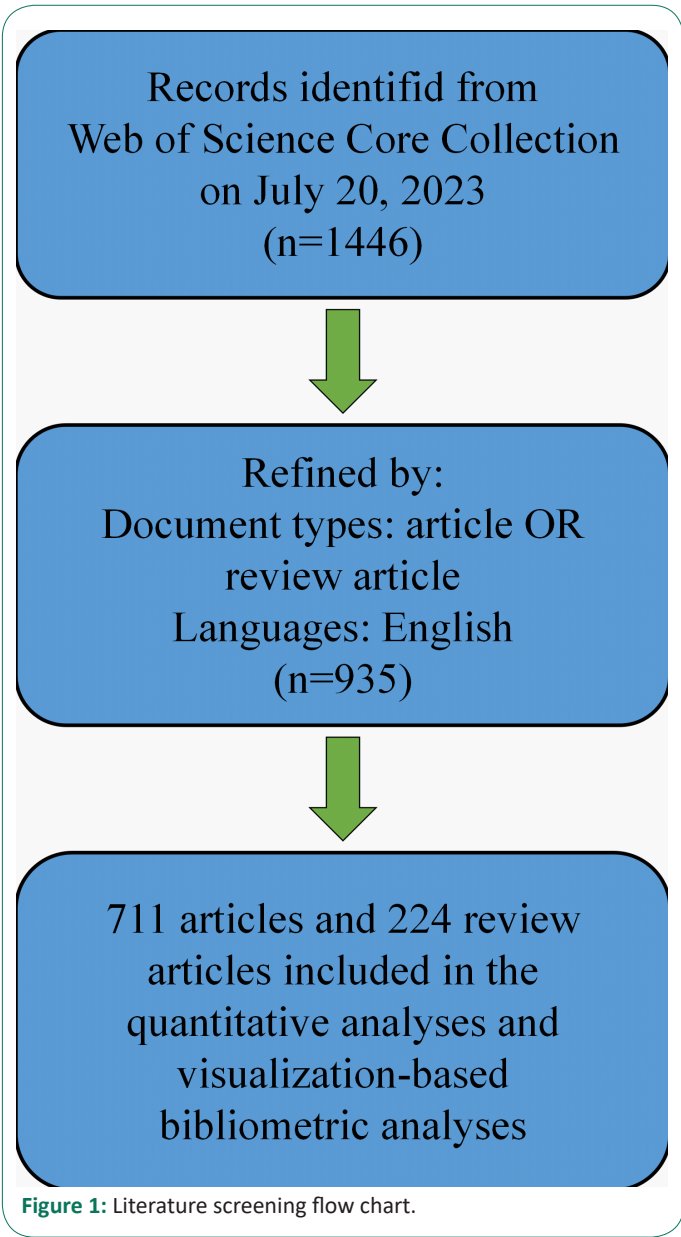
Figure 8A and Figure 8B show maps of co-cited references analysis and reference citation burst analysis, respectively. Of the 8098 cited references, 30 were cited at least 100 times. Among them, the most co-cited reference was the global first article, "Peroral endoscopic myotomy (POEM) for esophageal achalasia [5]," published in *Endoscopy* by Inoue Haruhiro et al. in 2010 (n=608) with the strongest bursts (strength=68.46). There were eight original articles and two reviews in the top ten references. On these highly cited references, the prospective multi-center results of POEM in treating achalasia, the efficacy comparison of POEM with PD and LHM in achalasia, and the studies based on the achalasia sub-type were attractive. It was worth noting that four references by Repici A et al. [16], Werner YB et al. [17], Ponds FA et al. [18], and Vaezi MF et al. [19] were still in a burst state.

### Keywords analysis

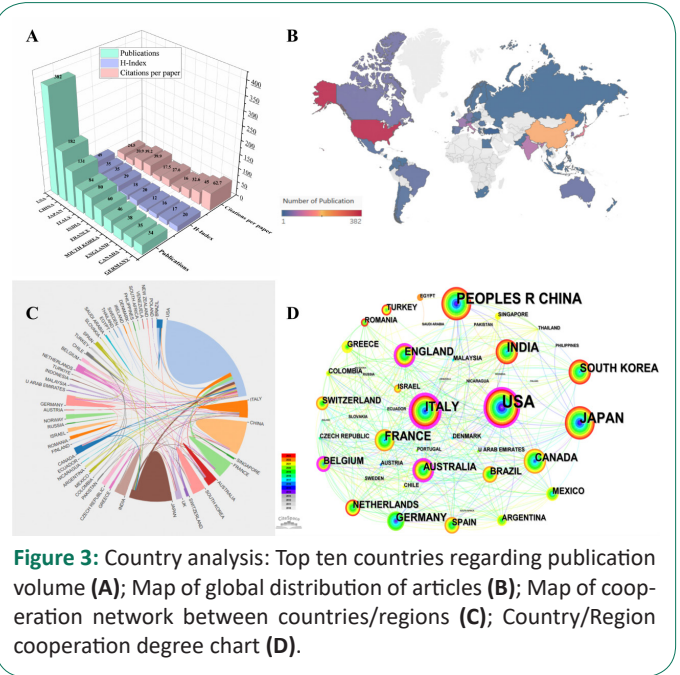
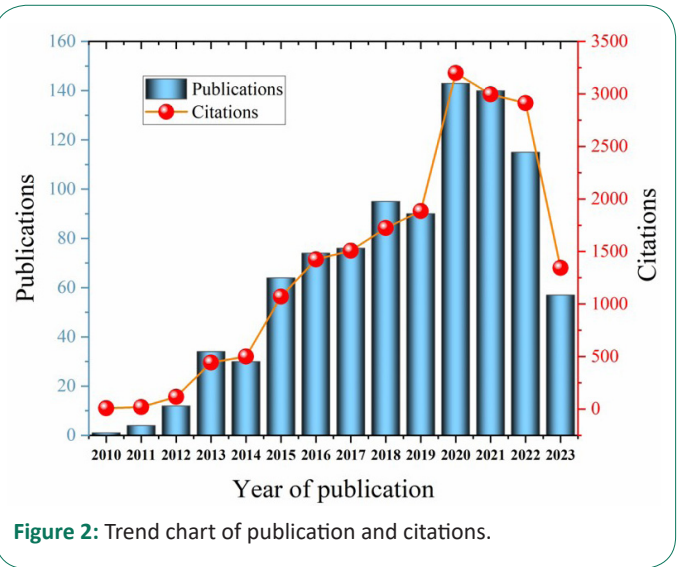
Keyword co-occurrence analysis reflects the current research status, including research hotspots and future directions. A co-occurrence network for high-frequency keywords is built in Figure 9A. In addition to the theme words "peroral endoscopic myotomy" and "achalasia," the keywords "Heller myotomy," "pneumatic dilatation," and "gastroesophageal reflux disease" ranked second, third, and fifth with 83,70, and 60 times, respectively. The results show that the efficacy comparison of POEM and traditional treatment and the occurrence of GERD after POEM have become the most prominent topics in this field. In addition, according to Figure 9B, keywords can be divided into 5 clusters: Cluster 1 (achalasia and its therapeutic modalities, including POEM, LHM, PD, etc.); Cluster 2 (extensive promotion of third space endoscopy, including G-POEM, Z-POEM, etc., green nodes); Cluster 3 (management of particular types of achalasia and other esophageal motility disorders, including the pediatric, the aged, the recurrent, the advanced, etc., blue nodes); Cluster 4 (POEM's safety and efficacy evaluation studies, including systematic review and meta-analysis, etc., yellow nodes); Cluster 5 (endoscopic functional luminal impedance planimetry application [EndoFlip] application, purple nodes). Moreover, we also visualized the year in which the keywords appeared with different colors (Figure 9C). "Zenker's diverticulum" and "epiphrenic diverticulum" were the latest keywords. Furthermore, we identify the top 19 strongest citations burst keywords from 2010 to 2023 in Figure 9D: esophagomyotomy (4.06, 2010-2017), endoscopic myotomy (4.84, 2012-2014), squamous cell carcinoma (2.79, 2013-2015), single center (12.72, 2014-2018), botulinum toxin (6.8, 2014-2015), experience (6.15, 2016-2017), meta-analysis (4.47, 2014-2018), prevalence (3.63, 2019-2023), pyloromyotomy G-POEM (3.56, 2019-2020), third space endoscopy (3.55, 2020-2023), lumen imaging probe (3.04, 2020-2023), zenkers diverticulum (3.71, 2021-2023), adverse event (3.63, 2021-2023), etc. It was worth noting that five keywords were still in a burst state.

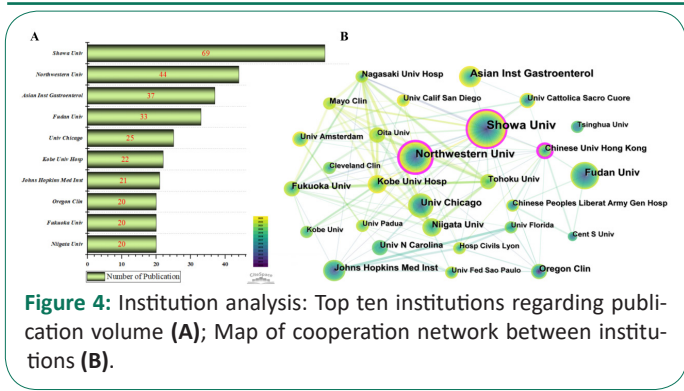
**Table 1:** The top ten source journals.

Rank	Journal	Publications	H-Index	Citations per paper	Quartile	Impact factor
1	Surgical Endoscopy	114	29	23.4	Q1	3.1
2	Gastrointestinal Endoscopy	54	25	36.7	Q1	7.7
3	Endoscopy	34	18	68.3	Q1	9.3
4	Digestive Endoscopy	29	12	21.7	Q2	5.3
5	Diseases of the Esophagus	27	11	17.1	Q4	2.6
6	Endoscopy International Open	27	6	8.3	-	2.6
7	World Journal of Gastroenterology	27	15	18.8	Q2	4.3
8	Journal of Laparoendoscopic & Advanced Surgical Techniques	25	7	7.6	Q4	1.3
9	Journal of Gastrointestinal Surgery	24	13	37.1	Q3	3.2
10	Neurogastroenterology and Motility	21	8	19.8	Q2	3.5

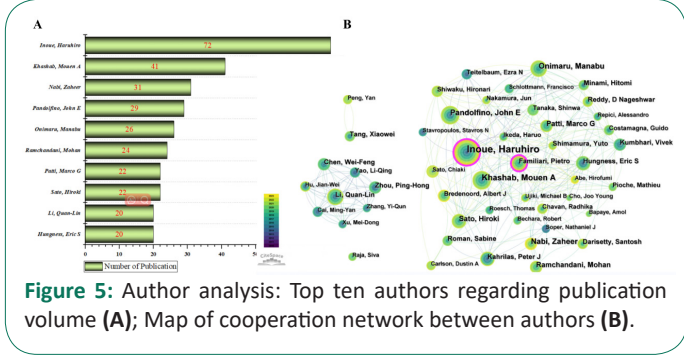


**Figure 1:** Literature screening flow chart.

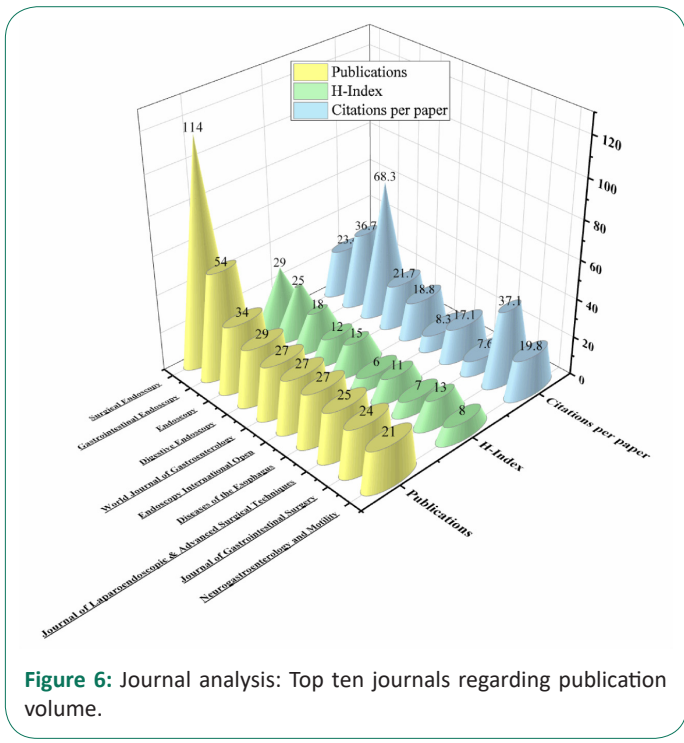




**Figure 4:** Institution analysis: Top ten institutions regarding publication volume (A); Map of cooperation network between institutions (B).



**Figure 5:** Author analysis: Top ten authors regarding publication volume (A); Map of cooperation network between authors (B).

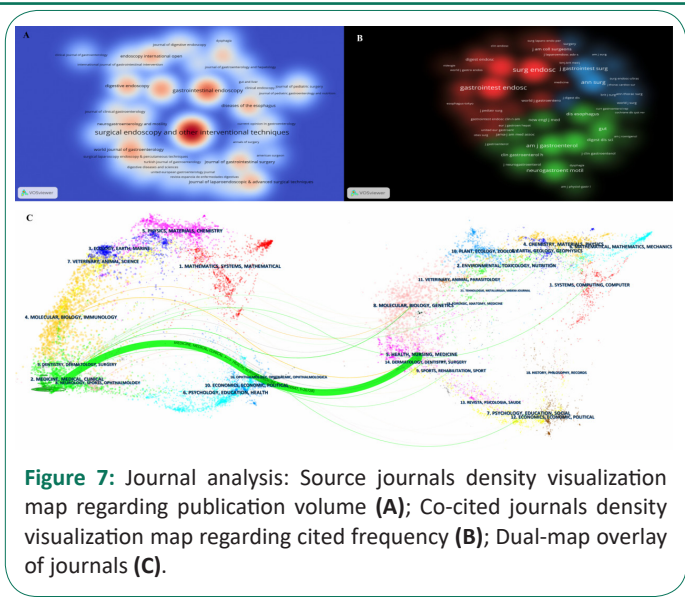


**Figure 6:** Journal analysis: Top ten journals regarding publication volume.

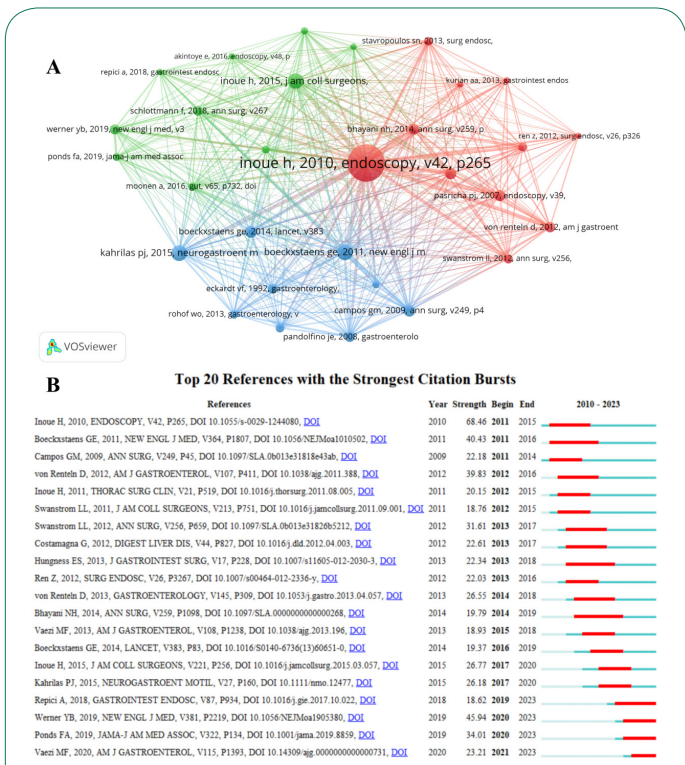
**Discussion**  
**General information**

With the help of bibliometrics, this study comprehensively analyzed the literature concerning POEM treatment of achalasia patients. A total of 935 articles published in 210 journals by 3592 authors from 1017 institutions in 50 countries were included in the analysis. Among the 935 articles, the number of original articles was more than three times that of review articles, which reflected a more significant focus by researchers on the original study rather than a review of this field. Our research showed that POEM has come a long way in the last thirteen years, but there is still a long way to go.

According to the publication trend, the development of this field in the decade 2010-2020 could be divided into a slow rise

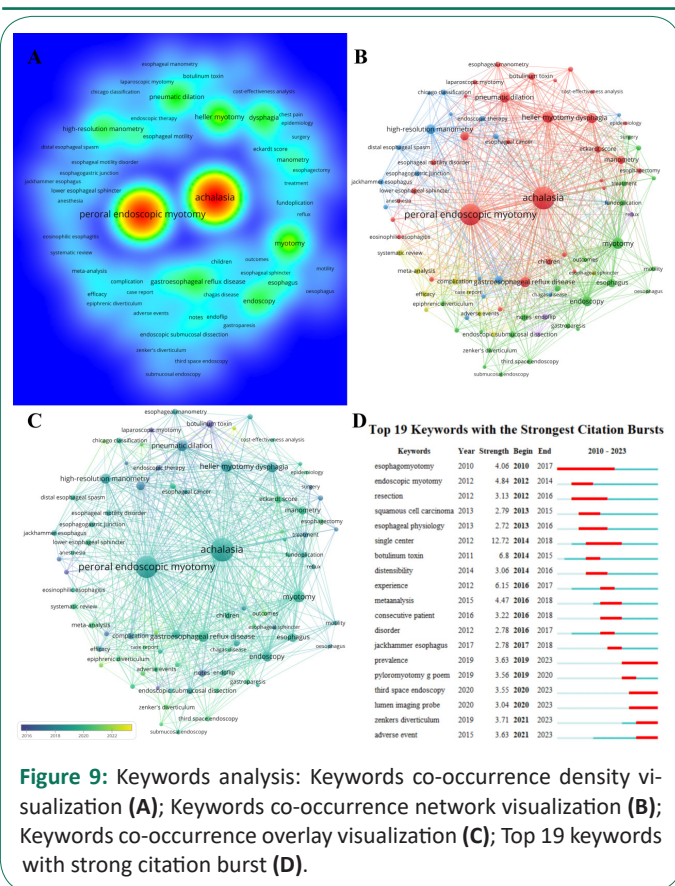


**Figure 7:** Journal analysis: Source journals density visualization map regarding publication volume (A); Co-cited journals density visualization map regarding cited frequency (B); Dual-map overlay of journals (C).



**Figure 8:** References analysis: References co-cited network visualization (A); Top ten references with strong citation burst (B).

in the early period (2010-2014) and a rapid rise in the late period (2015-2020). This change in development rate might be attributed to better diagnosis and management of achalasia by applying high-resolution manometry (HRM) and Chicago Classification version 3.0 in 2015 [20,21]. Moreover, articles reporting the promising efficacy and safety of POEM published between 2010 and 2014 had given confidence to endoscopists worldwide [22-24]. A growing number of publications indicated that POEM treatment of achalasia had attracted increasing attention and interest. However, it is worth noting that the growth in the publication number had stagnated since 2020, indicating that POEM's development in treating achalasia has hit a bottleneck. For example, in the face of the high incidence of GERD after POEM, there still needs to be an optimal prevention strategy [25]. Besides, faced with the challenge that the clinical success rate of POEM decreased over time, POEM is still nec-



**Figure 9:** Keywords analysis: Keywords co-occurrence density visualization (A); Keywords co-occurrence network visualization (B); Keywords co-occurrence overlay visualization (C); Top 19 keywords with strong citation burst (D).

essential to undergo the validation of long-term follow-up [26]. Furthermore, this also seems to result from the impact of the COVID-19 pandemic. It was reported that the number of POEM procedures in 2020 was significantly less than before COVID-19, which would also affect the study's progress and the publication of results [27].

The number of publications and centrality were crucial indicators in the country/institution/author analysis and the corresponding cooperation analysis. The USA, China, and Japan contributed most publications in this field. The USA had the most published articles, the highest H-index, and a high degree of centrality, leading the research in this field. China ranked second in the publication with the eighth-highest number of citations, indicating that the quality of research has yet to improve as the number of studies increases. Japan, the country that first proposed POEM, ranked third in publication volume and fourth in citation frequency, which indicates that Japan has a lasting and significant influence on this field. In addition, Germany, with the highest average citation number, and Italy, with the highest centrality, also played an essential role in developing this field.

In addition, we found on the publication map that many developing countries were still unresearched in this field. China and India, as representatives of developing countries, consistently lead the world in the number of published papers. However, their influence on other countries in this field needs to be stronger, reflected in the near isolation of Chinese mainland and India and corresponding institutions and authors in the cooperation network. There is a persistent imbalance between developed and developing countries. Partnerships between countries, institutions, and authors are crucial to developing the most reliable large-scale multi-center trials. In the future, the Chinese mainland and India still need to strengthen cooperation with other developed countries and become a link between developed and developing countries.

Of the top ten institutions, except for one from China and one from India, the remaining eight were half from Japan and half from the USA, which shows that building a first-class research institution is the key to improving the status of the country's academic community. Among them, Northwestern University in the USA had the highest centrality and played a vital "Bridge" role in global collaboration. Although Showa University in Japan also had a high degree of centrality, its cooperation was more limited to domestic institutional cooperation. Interestingly, in China, while the Chinese University of Hong Kong had extensive cooperation with the rest of the world, Fudan University, which had published the most papers, rarely cooperated with other institutions and only partially worked with domestic institutions. This contradiction may be because the Chinese mainland's cooperation with other countries and regions is relatively dispersed rather than concentrated. Either way, they have played a vital role in the global development of POEM for treating achalasia. Among the top ten authors, Inoue Haruhiro, the initiator of POEM, is the leader in this field. Through exchanges with scholars worldwide, he has extensively promoted the development of this field and made outstanding contributions to transforming the treatment of achalasia.

In journal analysis, *surgical endoscopy* was the most influential journal in this field regarding the combined results of publication volume and co-cited frequency. This might be due to the coincidence with the two characteristics of POEM: minimally invasive surgery (surgical) and endoscopic operation (endoscopy). *Endoscopy* and *Gastrointestinal Endoscopy* ranked in the top 3 sources and co-cited journals, indicating that they are essential in disseminating research in this field. The journal index generated by bibliometrics analysis can provide a reliable reference for researchers to search literature, and we suggest additional manuscripts to be submitted to these publications. *Endoscopy* has the highest number of citations per paper, probably because the article, "Peroral endoscopic myotomy (POEM) for esophageal achalasia [5]," with the highest number of citations (n=608) was published in this journal.

Regarding references citation burst analysis, four references were still in a burst state. In 2018, a meta-analysis by Repici A et al. showed that post-POEM gastroesophageal reflux disease (GERD) significantly increased compared with LHM plus fundoplication [16]. In 2019, a randomized trial study by Werner YB et al. concluded that POEM was comparable to LHM plus Dor's fundoplication for efficacy [17]. However, post-POEM gastroesophageal reflux was more common than LHM. Another randomized controlled trial conducted by Ponds FA et al. in 2019 found that POEM was more effective than PD and should be used as an initial treatment for patients with achalasia [18]. Last, in 2020, Vaezi MF et al. reported clinical guidelines for diagnosing and treating achalasia, recommending POEM, associated with a higher incidence of GERD, as the standard treatment protocol [19]. It could be found that the comparison of efficacy and the incidence of postoperative GERD between POEM and LHM were popular.

### The hotspots and trending comparison between POEM and LHM or PD

The comparison of POEM with traditional treatment methods LHM and PD is an evergreen tree in this field. The comparisons focused on clinical outcomes and the incidence of adverse events, particularly the occurrence of GERD of achalasia patients. Two randomized controlled trials have shown that compared with LHM with fundoplication, POEM has a similar effi-

cacy within two years follow-ups, with a shorter operation time and a higher incidence of GERD [17,28]. Due to the lack of anti-reflux procedures, the high incidence of GERD after POEM has been a problem. However, a new operation method of POEM with endoscopic fundoplication has been proposed recently [29]. Studies have reported that this is a safe and reproducible procedure that can reduce the occurrence of GERD in the short-term follow-up [30,31]. However, long-term follow-up results have yet to be discovered. Moreover, there need to be more clinical studies comparing POEM+F with LHM+F, which could be the way forward. More importantly, POEM also faces another major challenge of LHM. A study of 17 years of follow-up after LHM showed an effective rate of 79%, which is the level reported after five years of follow-up after POEM [32]. Therefore, the future research trend is comparing long-term follow-up results between POEM and LHM.

For PD, three randomized controlled trials have shown that POEM has a significant advantage in treatment-naïve patients, recurrent patients, and long-term follow-up outcomes of 5 years [18,33,34]. However, this should not lead to the abandonment of pneumatic dilation in clinical practice. Compared to POEM, PD is less time-consuming, easier to learn, and less likely to cause reflux esophagitis or reflux symptoms. In addition, PD does not require general anesthesia, thus shortening hospital stays. Ideally, all treatment options should be discussed with achalasia patients, and a joint decision should be made based on the patient's characteristics, for example, the subtype of achalasia, age, comorbidity, available expertise, and patient preferences [34].

#### **Particular achalasia patients and other esophageal motility disorders**

With the development of POEM technology, its application in the pediatric and the aged has gradually increased. Many studies have shown the safety and efficacy of POEM in these patients [35-38], but there need to be more studies comparing POEM with LHM or PD in special age groups. Besides, the clinical success rate for type III achalasia after traditional LHM and PD treatment has historically been limited [39]. POEM provides more effective and long-lasting relief for type III achalasia and should be considered a first-line treatment for this challenging sub-type [39,40]. In addition, POEM has good clinical efficacy and morphological improvement in treating patients with advanced achalasia With Sigmoid or Megaesophagus [41,42]. Furthermore, prior PD and LHM may make subsequent POEM treatment more challenging, but it does not impede successful POEM implementation and the safety and efficacy of achalasia patients [43,44]. POEM is a promising saving therapy for the failure of Heller myotomy and PD. Last, non-achalasia esophageal motility disorders include esophagogastric junction outflow obstruction, distal esophageal spasm, esophageal hyperconstriction, and other minor peristaltic disorders, which, although pathophysiologically different, present in a similar manner to achalasia [45,46]. Although it is not as effective as POEM in treating Achalasia, POEM is currently an effective treatment for these esophageal motility disorders [45,46]. Further work is needed to develop the best treatment strategies for such complex diseases.

#### **Systematic review and meta-analysis for POEM in treating achalasia**

With the publications of numerous case reports, case series, retrospective or prospective studies, single-center or multi-center

studies, single-arm or comparative or even randomized controlled trial studies on POEM in treating achalasia, systematic reviews, and meta-analyses based on these findings have also been published in large numbers, providing a large amount of evidence-based medical evidence in this field.

These pooled analyses focus on the following: 1) Short-term and long-term follow-up efficacy and safety [47,48]; 2) Comparison of clinical outcomes with LHM or PD [49,50]; 3) Comparison of efficacy and safety of different operation procedures [51,52]; 4) Group analysis based on Chicago classification [53]; 5) Special types of achalasia [54,55]; 6) The occurrence and possible risk factors of GERD [56,57]; 7) Factors for predicting clinical outcomes [58]; 8) Learning curve [59]; 9) Analysis based on randomized controlled trial studies [60]; 10) Treatment of non-achalasia, including other esophageal motility disorders [61], refractory gastroparesis [62], zenker's diverticulum [63], etc. Notably, a high-quality, randomized, controlled trial-based network meta-analysis published in the *Lancet Gastroenterology & Hepatology* shows concluded that POEM and LHM should be the preferred treatments for idiopathic achalasia, while POEM was ranked first [60]. Antibiotic use, anesthesia management, POEM with endoscopic fundoplication, and EndoFlip applications may be potential research hotspots for future meta-analysis.

#### **EndoFlip application**

The EndoFlip is a catheter-based tool that uses impedance planimetry to obtain objective measurements of the gastro-esophageal junction, including cross-sectional area, distensibility index, and compliance [64]. Over time, the role of EndoFlip in POEM for treating achalasia has expanded, and it has been found useful when performed before POEM, during POEM, and postoperative monitoring and follow-up [64-69]. Doing this before POEM can determine if the patient's measurements are consistent with those of patients with achalasia. The intraoperative addition of EndoFlip technology provides real-time feedback on the adequacy of the myotomy, enabling tailored myotomy. Key outcome measures of POEM in treating achalasia are effective in alleviating symptoms and preventing pathological gastroesophageal reflux. Changes in cross-sectional area, dilatation index, and compliance measured after POEM by EndoFlip are associated with clinical response and postoperative reflux in patients with achalasia [64-69]. So far, multiple authors have attempted to get the ideal range of parameters to achieve the goal of myotomy. However, differences in measurement protocols limit direct comparisons between the inconsistent results published by different studies [64-69]. Therefore, the parameters that best guide endoscopists to select the appropriate length and range of myotomy, which can alleviate the achalasia and reduce postoperative GERD, need to be clarified. The research in this area needs to be further in-depth.

POEM for the treatment of achalasia opens the door to third-space endoscopy techniques [70]. The third-space endoscopy technique, also known as the submucosal endoscopic technique, allows for a wide range of therapeutic interventions in the submucosa, even the muscular or subserous layer that enters the lumen of the digestive tract [71]. The development of POEM in treating achalasia has revolutionized the field of therapeutic endoscopy, and its methods are constantly improved and perfected. Using the same steps as POEM, namely constructing submucosal tunnels and safely closing mucosal incisions, POEM has yielded some effective derivatives, such as such as peroral endoscopic tumor resection or submucosal tunneling endoscopic resection for resection of subepithelial tumors, Z-POEM

for Zenker's diverticulum, D-POEM for epiphrenic diverticula, and G-POEM for refractory gastroparesis [72]. Of course, this application is not limited to the upper digestive tract. For example, POEM is also used in the lower digestive tract to treat congenital megacolon or perform rectal surgery [72]. Submucosal tunneling technology has been widely accepted and continues to evolve. Indications for third-space endoscopic surgery are proliferating due to its non-invasive nature, which may diminish the impact of surgical operation. Besides, more researches are needed to prove the safety and effectiveness of these techniques.

There were some shortcomings in our study. First, we only conducted a literature search on the WOSCC database. Other available literature databases, such as Scopus, Medline, and Google Scholar, were not searched. Furthermore, it was limited to original articles and reviews published in English. These might restrict the generality of the findings. Second, the number of citations was an index to judge the influence of individuals, but many factors affected the number of citations. For example, articles published earlier were likely to have more citations. In addition, self-citation, incomplete citation, and omission were essential factors affecting citation frequency. This was the inherent flaw of citation analysis.

POEM, a representative of orifice transluminal endoscopic surgery, has become a first-line treatment for achalasia. POEM has come a long way in the last thirteen years, but there is still a long way to go. Comparison between POEM and laparoscopic Heller myotomy or pneumatic dilation, particular achalasia patients and other esophageal motility disorders, systematic review and meta-analysis, endoscopic functional luminal impedance planimetry application, and third space endoscopy were research hotspots and future direction.

### Declarations

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### References

1. Pandolfino JE, Carlson DA, McGarva J, et al. Validation of the Achalasia Patient-Reported Outcomes Questionnaire. *Aliment Pharmacol Ther.* 2022; 56(10): 1434-1443.
2. Harvey PR, Thomas T, Chandan JS, et al. Incidence, morbidity and mortality of patients with achalasia in England: findings from a study of nationwide hospital and primary care data. *Gut.* 2019; 68(5): 790-795.
3. Yaghoobi M, Mayrand S, Martel M, Roshan-Afshar I, Bijarchi R, Barkun A. Laparoscopic Heller's myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized, controlled trials. *Gastrointest Endosc.* 2013; 78(3): 468-475.
4. Kuipers T, Ponds FA, Fockens P, et al. Peroral endoscopic myotomy versus pneumatic dilation in treatment-naive patients with achalasia: 5-year follow-up of a randomised controlled trial. *Lancet Gastroenterol Hepatol.* 2022; 7(12): 1103-1111.
5. Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy.* 2010; 42(4): 265-271.

6. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. *Am J Gastroenterol.* 2020; 115(9): 1393-1411.
7. Xia H, Tan S, Huang S, et al. Scoping Review and Bibliometric Analysis of the Most Influential Publications in Achalasia Research from 1995 to 2020. *Biomed Res Int.* 2021; 2021: 8836395.
8. Liu XY, Chen WF, He MJ, et al. Publication trends of peroral endoscopic myotomy during 2010-2022: a bibliometric analysis. *Ann Transl Med.* 2022; 10(23): 1272.
9. Pritchard A. Statistical bibliography or bibliometrics? *J Doc.* (1969) 25: 348-9.
10. Berta A, Miguel Ángel C, Clara GS, Rubén H. A bibliometric analysis of 10 years of research on symptom networks in psychopathology and mental health. *Psychiatry Res.* 2022; 308: 114380.
11. Wang S, Zhou H, Zheng L, et al. Global Trends in Research of Macrophages Associated With Acute Lung Injury Over Past 10 Years: A Bibliometric Analysis. *Front Immunol.* 2021; 12: 669539.
12. Teles RHG, Morales HF, Cominetti MR. Global trends in nanomedicine research on triple negative breast cancer: a bibliometric analysis. *Int J Nanomedicine.* 2018; 13: 2321-2336.
13. Zhang XD, Zhang Y, Zhao YZ, Zhou CH, Zou DW. Autoimmune pancreatitis: A bibliometric analysis from 2002 to 2022. *Front Immunol.* 2023; 14: 1135096.
14. Dai YK, Zhao ZM, Liu C. Treatment of Liver Fibrosis: A 20-Year Bibliometric and Knowledge-Map Analysis. *Front Pharmacol.* 2022; 13: 942841.
15. Xia C, Yin H, Zhang K, Wang Z, Yang X, Huang H. The global research status and trends of the application of endoscopic ultrasonography in pancreatic tumors over the last decades: A bibliometric study. *Front Oncol.* 2022; 12: 980415.
16. Repici A, Fuccio L, Maselli R, et al. GERD after per-oral endoscopic myotomy as compared with Heller's myotomy with fundoplication: a systematic review with meta-analysis. *Gastrointest Endosc.* 2018; 87(4): 934-943.e18.
17. Werner YB, Hakanson B, Martinek J, et al. Endoscopic or Surgical Myotomy in Patients with Idiopathic Achalasia. *N Engl J Med.* 2019; 381(23): 2219-2229.
18. Ponds FA, Fockens P, Lei A, et al. Effect of Peroral Endoscopic Myotomy vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes Among Treatment-Naive Patients With Achalasia: A Randomized Clinical Trial. *JAMA.* 2019; 322(2): 134-144.
19. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. *Am J Gastroenterol.* 2020; 115(9): 1393-1411.
20. Greene CL, Chang EJ, Oh DS, Worrell SG, Hagen JA, DeMeester SR. High resolution manometry sub-classification of Achalasia: does it really matter? Does Achalasia sub-classification matter?. *Surg Endosc.* 2015; 29(6): 1363-1367.
21. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil.* 2015; 27(2): 160-174.
22. Costamagna G, Marchese M, Familiari P, Tringali A, Inoue H, Perri V. Peroral endoscopic myotomy (POEM) for oesophageal achalasia: preliminary results in humans. *Dig Liver Dis.* 2012; 44(10): 827-832.
23. Von Renteln D, Fuchs KH, Fockens P, et al. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. *Gastroenterology.* 2013; 145(2):



- 309-11.e113.
24. Minami H, Isomoto H, Yamaguchi N, et al. Peroral endoscopic myotomy for esophageal achalasia: clinical impact of 28 cases. *Dig Endosc.* 2014; 26(1): 43-51.
  25. Teh JL, Tham HY, Soh AYS, et al. Gastro-esophageal reflux disease (GERD) after peroral endoscopic myotomy (POEM). *Surg Endosc.* 2022; 36(5): 3308-3316.
  26. Zhang H, Zeng X, Huang S, et al. Mid-Term and Long-Term Outcomes of Peroral Endoscopic Myotomy for the Treatment of Achalasia: A Systematic Review and Meta-Analysis. *Dig Dis Sci.* 2023; 68(4): 1386-1396.
  27. Ominami M, Sato H, Fujiyoshi Y, et al. Impact of the COVID-19 pandemic on high-resolution manometry and peroral endoscopic myotomy for esophageal motility disorder in Japan. *Dig Endosc.* 2022; 34(4): 769-777.
  28. de Moura ETH, Jukemura J, Ribeiro IB, et al. Peroral endoscopic myotomy vs laparoscopic myotomy and partial fundoplication for esophageal achalasia: A single-center randomized controlled trial. *World J Gastroenterol.* 2022; 28(33): 4875-4889.
  29. Inoue H, Ueno A, Shimamura Y, et al. Peroral endoscopic myotomy and fundoplication: a novel NOTES procedure. *Endoscopy.* 2019; 51(2): 161-164.
  30. Bapaye A, Dashatwar P, Dharamsi S, Pujari R, Gadhikar H. Single-session endoscopic fundoplication after peroral endoscopic myotomy (POEM+F) for prevention of post gastroesophageal reflux - 1-year follow-up study. *Endoscopy.* 2021; 53(11): 1114-1121.
  31. Shrigiriwar A, Zhang LY, Ghandour B, et al. Technical details and outcomes of peroral endoscopic myotomy with fundoplication: the first U.S. experience (with video). *Gastrointest Endosc.* 2023; 97(3): 585-593.
  32. Csendes A, Orellana O, Figueroa M, Lanzarini E, Panza B. Long-term (17 years) subjective and objective evaluation of the durability of laparoscopic Heller esophagomyotomy in patients with achalasia of the esophagus (90% of follow-up): a real challenge to POEM. *Surg Endosc.* 2022; 36(1): 282-291.
  33. Saleh CMG, Familiari P, Bastiaansen BAJ, et al. The Efficacy of Peroral Endoscopic Myotomy vs Pneumatic Dilation as Treatment for Patients With Achalasia Suffering From Persistent or Recurrent Symptoms After Laparoscopic Heller Myotomy: A Randomized Clinical Trial. *Gastroenterology.* 2023; 164(7): 1108-1118.e3.
  34. Kuipers T, Ponds FA, Fockens P, et al. Peroral endoscopic myotomy versus pneumatic dilation in treatment-naive patients with achalasia: 5-year follow-up of a randomised controlled trial. *Lancet Gastroenterol Hepatol.* 2022; 7(12): 1103-1111.
  35. Chen WF, Li QL, Zhou PH, et al. Long-term outcomes of peroral endoscopic myotomy for achalasia in pediatric patients: a prospective, single-center study. *Gastrointest Endosc.* 2015; 81(1): 91-100.
  36. Nabi Z, Ramchandani M, Chavan R, et al. Outcome of peroral endoscopic myotomy in children with achalasia. *Surg Endosc.* 2019; 33(11): 3656-3664.
  37. Li CJ, Tan YY, Wang XH, Liu DL. Peroral endoscopic myotomy for achalasia in patients aged  $\geq 65$  years. *World J Gastroenterol.* 2015; 21(30): 9175-9181.
  38. Mari A, Sbeit W, Abboud W, Awadie H, Khoury T. Achalasia in the Elderly: Diagnostic Approach and a Proposed Treatment Algorithm Based on a Comprehensive Literature Review. *J Clin Med.* 2021; 10(23): 5565.
  39. Sudarshan M, Raja S, Adhikari S, et al. Peroral endoscopic myotomy provides effective palliation in type III achalasia. *J Thorac Cardiovasc Surg.* 2022; 163(2): 512-519.e1.
  40. Zhang W, Linghu EQ. Peroral Endoscopic Myotomy for Type III Achalasia of Chicago Classification: Outcomes with a Minimum Follow-Up of 24 Months. *J Gastrointest Surg.* 2017; 21(5): 785-791.
  41. Yoon HJ, Lee JE, Jung DH, Park JC, Youn YH, Park H. Morphologic Restoration After Peroral Endoscopic Myotomy in Sigmoid-type Achalasia. *J Neurogastroenterol Motil.* 2020; 26(1): 67-73.
  42. Mandavdhare HS, M PK, Shukla J, Kumar A, Sharma V. Role of Peroral Endoscopic Myotomy in Advanced Achalasia Cardia With Sigmoid and/or Megaesophagus: A Systematic Review and Metaanalysis. *J Neurogastroenterol Motil.* 2022; 28(1): 15-27.
  43. Jin H, Wang B, Zheng ZQ, et al. Peroral endoscopic myotomy for the treatment of achalasia after failed pneumatic dilation. *Surg Endosc.* 2021; 35(12): 6960-6968.
  44. Zhou PH, Li QL, Yao LQ, et al. Peroral endoscopic remyotomy for failed Heller myotomy: a prospective single-center study. *Endoscopy.* 2013; 45(3): 161-166.
  45. Filicori F, Dunst CM, Sharata A, et al. Long-term outcomes following POEM for non-achalasia motility disorders of the esophagus. *Surg Endosc.* 2019; 33(5): 1632-1639.
  46. Bernardot L, Roman S, Barret M, et al. Efficacy of per-oral endoscopic myotomy for the treatment of non-achalasia esophageal motor disorders. *Surg Endosc.* 2020; 34(12): 5508-5515.
  47. Barbieri LA, Hassan C, Rosati R, Romario UF, Correale L, Repici A. Systematic review and meta-analysis: Efficacy and safety of POEM for achalasia. *United European Gastroenterol J.* 2015; 3(4): 325-334.
  48. Vespa E, Pellegatta G, Chandrasekar VT, et al. Long-term outcomes of peroral endoscopic myotomy for achalasia: a systematic review and meta-analysis. *Endoscopy.* 2023; 55(2): 167-175.
  49. Schlottmann F, Lockett DJ, Fine J, Shaheen NJ, Patti MG. Laparoscopic Heller Myotomy Versus Peroral Endoscopic Myotomy (POEM) for Achalasia: A Systematic Review and Meta-analysis. *Ann Surg.* 2018; 267(3): 451-460.
  50. Zhong C, Tan S, Huang S, et al. Peroral endoscopic myotomy versus pneumatic dilation for achalasia: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2020; 32(11): 1413-1421.
  51. Mohan BP, Ofosu A, Chandan S, et al. Anterior versus posterior approach in peroral endoscopic myotomy (POEM): a systematic review and meta-analysis. *Endoscopy.* 2020; 52(4): 251-258.
  52. Nabi Z, Talukdar R, Mandavdhare H, Reddy DN. Short versus long esophageal myotomy during peroral endoscopic myotomy: A systematic review and meta-analysis of comparative trials. *Saudi J Gastroenterol.* 2022; 28(4): 261-267.
  53. Andolfi C, Fisichella PM. Meta-analysis of clinical outcome after treatment for achalasia based on manometric subtypes. *Br J Surg.* 2019; 106(4): 332-341.
  54. Lee Y, Brar K, Doumouras AG, Hong D. Peroral endoscopic myotomy (POEM) for the treatment of pediatric achalasia: a systematic review and meta-analysis. *Surg Endosc.* 2019; 33(6): 1710-1720.
  55. Huang Z, Cui Y, Li Y, Chen M, Xing X. Peroral endoscopic myotomy for patients with achalasia with previous Heller myotomy: a systematic review and meta-analysis. *Gastrointest Endosc.* 2021; 93(1): 47-56.e5.

56. Repici A, Fuccio L, Maselli R, et al. GERD after per-oral endoscopic myotomy as compared with Heller's myotomy with fundoplication: a systematic review with meta-analysis. *Gastrointest Endosc.* 2018; 87(4): 934-943.e18.
57. Mota RCL, de Moura EGH, de Moura DTH, et al. Risk factors for gastroesophageal reflux after POEM for achalasia: a systematic review and meta-analysis. *Surg Endosc.* 2021; 35(1): 383-397.
58. Oude Nijhuis RAB, Prins LI, Mostafavi N, van Etten-Jamaludin FS, Smout AJPM, Bredenoord AJ. Factors Associated With Achalasia Treatment Outcomes: Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol.* 2020; 18(7): 1442-1453.
59. Puli SR, Wagh MS, Forcione D, Gopakumar H. Learning curve for esophageal peroral endoscopic myotomy: a systematic review and meta-analysis. *Endoscopy.* 2023; 55(4): 355-360.
60. Mundre P, Black CJ, Mohammed N, Ford AC. Efficacy of surgical or endoscopic treatment of idiopathic achalasia: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol.* 2021; 6(1): 30-38.
61. Khan MA, Kumbhari V, Ngamruengphong S, et al. Is POEM the Answer for Management of Spastic Esophageal Disorders? A Systematic Review and Meta-Analysis. *Dig Dis Sci.* 2017; 62(1): 35-44.
62. Kamal F, Khan MA, Lee-Smith W, et al. Systematic review with meta-analysis: one-year outcomes of gastric peroral endoscopic myotomy for refractory gastroparesis. *Aliment Pharmacol Ther.* 2022; 55(2): 168-177.
63. Zhang H, Huang S, Xia H, et al. The role of peroral endoscopic myotomy for Zenker's diverticulum: a systematic review and meta-analysis. *Surg Endosc.* 2022; 36(5): 2749-2759.
64. Familiari P, Gigante G, Marchese M, et al. EndoFLIP system for the intraoperative evaluation of peroral endoscopic myotomy. *United European Gastroenterol J.* 2014; 2(2): 77-83.
65. Yoo IK, Choi SA, Kim WH, Hong SP, Cakir OO, Cho JY. Assessment of Clinical Outcomes after Peroral Endoscopic Myotomy via Esophageal Distensibility Measurements with the Endoluminal Functional Lumen Imaging Probe. *Gut Liver.* 2019; 13(1): 32-39.
66. Su B, Callahan ZM, Novak S, Kuchta K, Ujiki MB. Using Impedance Planimetry (EndoFLIP) to Evaluate Myotomy and Predict Outcomes After Surgery for Achalasia. *J Gastrointest Surg.* 2020; 24(4): 964-971.
67. Attaar M, Wong HJ, Wu H, et al. Changes in impedance planimetry (EndoFLIP) measurements at follow-up after peroral endoscopic myotomy (POEM). *Surg Endosc.* 2022; 36(12): 9410-9415.
68. Attaar M, Su B, Wong HJ, et al. Intraoperative impedance planimetry (EndoFLIP™) results and development of esophagitis in patients undergoing peroral endoscopic myotomy (POEM). *Surg Endosc.* 2021; 35(8): 4555-4562.
69. Amundson JR, Wu H, VanDruff V, et al. Esophagogastric junction compliance on impedance planimetry (EndoFLIP™) following peroral endoscopic myotomy (POEM) predicts improvement in postoperative eckardt score. *Surg Endosc.* 2023; 37(2): 1493-1500.
70. Inoue H, Maydeo A. Peroral endoscopic myotomy (POEM) opens the door of third-space endoscopy. *Endoscopy.* 2019; 51(11): 1010-1012.
71. Shimamura Y, Fujiyoshi Y, Fujiyoshi MRA, Inoue H. Evolving field of third-space endoscopy: Derivatives of peroral endoscopic myotomy. *Dig Endosc.* 2023; 35(2): 162-172.
72. Teitelbaum EN, Swanstrom LL. Submucosal surgery: novel interventions in the third space. *Lancet Gastroenterol Hepatol.* 2018; 3(2): 134-140.