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Does Anti-Reflux Surgery Improve Outcomes in Isolated Laryngopharyngeal Reflux? A Systematic Review

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Abstract

Purpose of review Laryngopharyngeal Reflux (LPR) continues to challenge management due to its uncertain pathological mechanism, variable clinical manifestations, and inconsistent treatment outcomes. Anti Reflux surgery (ARS), specifically fundoplication, is a well described efficacious treatment for patients with proven gastroesophageal reflux disease, who fail lifestyle modification and medical therapy. However, patients with upper aerodigestive tract symptoms attributed to 'isolated LPR,' where there is no objective and/or symptomatic distal GORD, are a difficult cohort to provide an effective, durable and reproducible treatment. This review aims to assess the literature evidence for ARS in the treatment of patients with 'isolated LPR'.

Recent findings Five studies from 689 initial records met the inclusion criteria. Treatment effect was primarily evaluated through patient reported outcome measures. There was a wide range in the percentage of patients who achieved complete symptom resolution (30–91%) of LPR symptoms following laparoscopic anti-reflux surgery. There was a general trend towards greater symptom improvement in patients with combination of LPR and GORD following ARS.

Summary The current evidence does not show a clear benefit in ARS for the treatment of isolated LPR. Further study on the correct identification of patients with LPR are required to better predict patiets who would benefit from fundoplication.

Keywords Laryngopharyngeal reflux · Fundoplication · Anti reflux surgery · Gastro-oesophageal reflux · Treatment outcome

Introduction

Laryngopharyngeal Reflux (LPR) is an inflammatory condition of the upper aerodigestive tract which manifests with a constellation of heterogenous symptoms such chronic cough, sore throat, globus pharyngeus, chronic cough, dysphonia, and frequent clearing of phlegm [1]. Manifestations of other extra-oesophageal diseases implicated in LPR include asthma, bronchitis, vocal granuloma, dental disease and laryngeal cancer [2, 3]. The true incidence of LPR is unknown but 10–30% of the population in Western society are estimated to be affected [4, 5]. Indeed, more than 50% of Koufman and colleagues' series of 113 consecutive patients with laryngeal symptoms referred to their Ear Nose and Throat Clinic were ultimately diagnosed with LPR [6].

Traditionally, LPR was considered a secondary consequence of gastric and/or duodenal content refluxing to the larynx, pharynx and nasal passages causing chronic mucosal injury [7]. Patients who suffer from acid reflux based LPR symptoms are often labelled as 'silent reflux' or 'extra-oesophageal symptoms of GORD' in the literature. Whilst the oesophageal mucosa can resist up to 50 acid reflux episodes before mucosal injury, the upper aerodigestive tract is demonstrably more sensitive, with injury after only 4 reflux episodes [8]. Heartburn, a common complaint among patients with gastro-oesophageal reflux (GORD), is however, not often reported in LPR. In contrast, the 'reflex theory' postulates that exposure of gastric contents to the

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distal oesophagus stimulate the embryologically common vagal pathway between the oesophagus and the bronchial tree leading to cough, throat clearing, and airway inflammation and a vicious cycle of further propagation of symptoms [9]. Abnormal aerosolization of activated pepsin, and bile acids reaching the upper aerodigestive tract are also implicated [10, 11].

The lack of a single underlying mechanism that unites all patients with LPR often leads to delay in diagnosis, as does the lack of a universal diagnostic criteria. In clinical practice, patient-reported-outcome-measures such as the Reflux Symptom Index (RSI) by Belafsky and colleagues [12] are used as part of a diagnostic algorithm, and to evaluate treatment effect. Suspected LPR patients trial proton-pump inhibitor (PPI) therapy and undergo a combination of endoscopy, high resolution manometry, oesophageal multichannel intraluminal impedance, and 24-hour pH monitoring. Most studies advocate for a balance of investigation modalities that have a high sensitivity for reflux assessment (both acid and non-acidic), and interrogation of the pharynx [13].

The goals of anti-reflux surgery in repairing the mechanical and physiological barriers which prevent reflux, would logically improve 'reflux-induced' LPR symptoms. Several systematic reviews have reported on this positive, but not definitive, role of ARS in LPR [5, 14, 15]. There is however a significant population of LPR patients for whom, there is no measurable distal GORD. The true size of this patient population has not been clearly defined by virtue of underdiagnosis and under-reporting but concerningly has been reported as high as 47% of all LPR [16]. Most case series which report on ARS in LPR have not specifically studied this patient subpopulation. Our review aims to evaluate the evidence in the literature for the role of ARS in the treatment of this challenging patient cohort.

Method

Original articles reporting on the outcomes of fundoplication on adult patients diagnosed with LPR were identified for analysis. Subjectively, LPR was defined as either a reported RSI score of 13 or above and/or if patients had symptoms consistent with LPR. Given the difficulty of diagnosing LPR, the diagnostic methodology was not defined. There is no widely adopted definition for the phenotype of 'Isolated LPR' in the literature. With respect to clinical applicability of the review findings, the following two groups of patients were therefore considered to satisfy the inclusion criteria: [1] cohorts where symptomatic LPR was the only indication for undergoing ARS and [2] cohorts where LPR patients had objective evidence of a normal distal oesophageal reflux profile. Studies where the characteristics of the cohort with isolated LPR could not clearly be delineated were excluded. This included several studies where "isolated LPR' population cohorts were selected for ARS in study protocols, but the subsequent results section did not provide specific diagnostic or outcome details on this cohort. Reviews, meta-analyses, case reports and opinions were excluded as were paediatric patients, animal and cadaveric studies.

Outcomes

Outcome of ARS was primarily assessed using the Reflux Symptom Index. 'Symptom free' was defined as a complete normalisation of upper aerodigestive tract symptoms compared to baseline. 'Symptom improvement' described the ongoing presence of some or all LPR symptoms but with improvement compared to baseline.

Search Strategy

The search strategy was performed on the following medical databases: Ovid Medline (1946 to December 2024), Ovid EMBASE (1947 to present), Cochrane database, PubMed (1946 to present) and Google Scholar. The search strategy was executed by 2 authors independently (RDS and AH). The primary search domains were LPR and Fundoplication. Search terms for LPR included 'laryngopharyngeal reflux' (MESH), 'laryngopharyngeal', 'extraesophageal', 'extra-esophageal', 'reflux laryngitis', 'supra-esophageal', 'supra-oesophageal' and 'supraesophageal'. Search terms for fundoplication included 'Fundoplication' (MESH), 'fundoplication', 'anti-reflux surgery', 'antireflux surgery', AND 'transoral incisionless fundoplication'. The two domains were combined using the 'AND' operator. Additional references were obtained by screening the reference lists of selected articles or from review publications. Prospective or retrospective, case-controlled, cohort or randomised controlled studies published between 1980 and 2024 December were considered. Studies were limited to those published in English language peer-reviewed journals. The systematic review was performed according to the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17] (Fig. 1).

The selected studies were assessed for potential bias using the 'Tool to assess risk of bias in cohort studies' developed by the CLARITY Group at McMaster University [18] (Table 1).

Data Extraction

In each of the selected studies the following variables were extracted: study type, number of patients, method of LPR diagnosis, control group (patients with concurrent GORD),

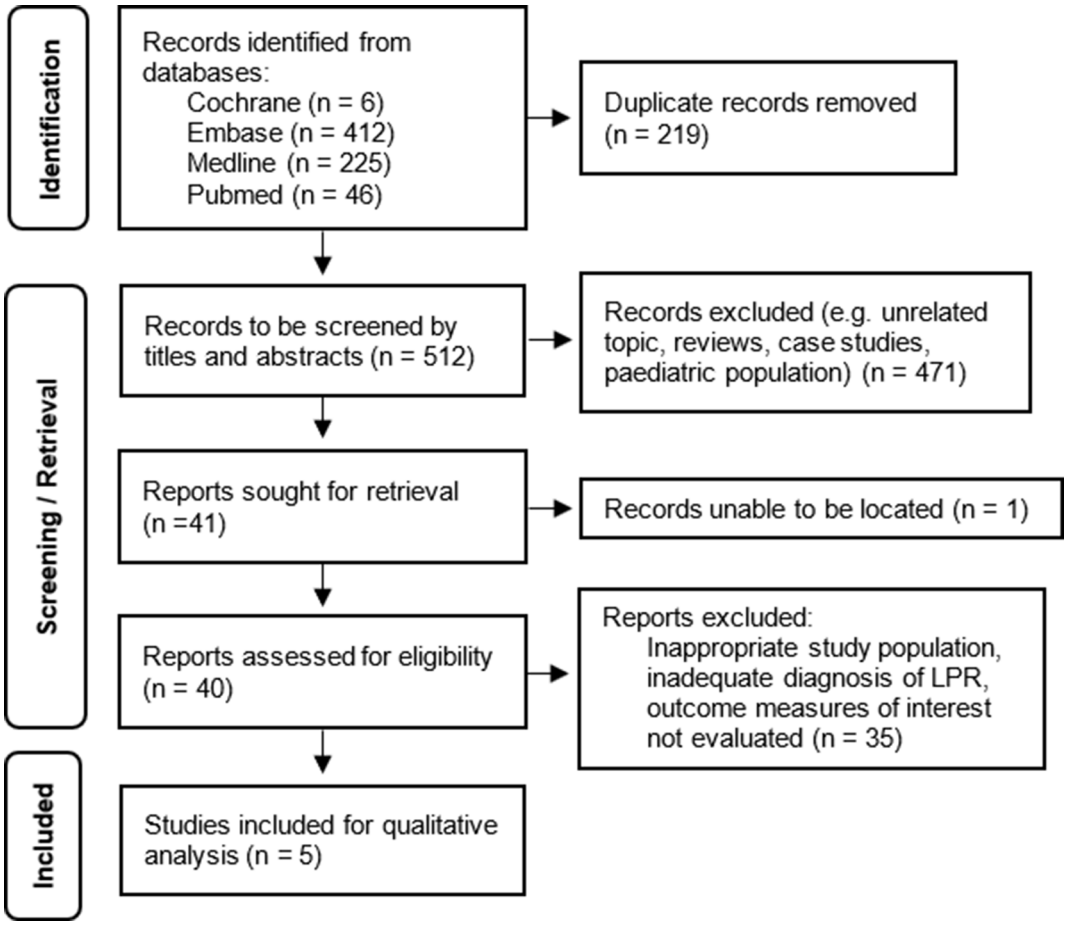

Fig. 1 PRISMA flowchart

Table 1 Assessment of risk of bias in included studies

Study	LPR Diagnosis	Exclusion Criteria	Outcomes definition	Subjective findings	Objective findings	Outcome blinding	Appropriate follow up
Catania et al, 2007	Yes	Probably Yes	Yes	Yes	No	No	Yes
Ratnasingam et al, 2011	Probably Yes	Yes	Probably Yes	No	No	No	Yes
Aiolfi et al, 2020	Probably Yes	Yes	Yes	Yes	No	No	Probably Yes
Falk et al, 2020	Probably Yes	Yes	Yes	Probably Yes	No	No	Yes
Suzuki et al, 2022	Yes	Yes	Yes	Yes	Yes	No	Yes

type of fundoplication, preoperative and postoperative RSI, period of follow up and percentage of patients free of symptoms.

Results

The characteristics and key results of the five studies included for analysis are summarised in Table 2.

Demographics

Of the five studies evaluated, two were single centre prospective trials, one single centre controlled prospective trial and two single centre retrospective trials. Suzuki et al., had the smallest cohort of eight patients, Ratnasingam et al. had identified 27 isolated LPR patients and 66 LPR/GORD patients within a larger patient cohort of 893 who underwent ARS. The remaining three cohorts were ranged from 61 to 90 patients of variable ‘isolated LPR’ and combined ‘LPR/GORD’ cohorts.

Table 2 Summary of inclusion study characteristics and outcomes

Study (design)	Characteristics	Intervention	Preoperative disease severity	Postop disease severity	% symptom free
Catania et al., 2007 *(SP)*	Total $n=61$, 42 F, mean age 58 Symptom groups LPR $n=24$ LPR/GORD $n=37$	LNF	RSI mean for entire cohort 31.5 +/- 7.4	RSI mean for entire cohort at 2 years 10.5 +/- 7.8 $P<0.01$ Symptoms improved LPR 67% LPR/GORD 81%	LPR 60% ($n=14$), LPR/GORD 65% ($n=24$)
Ratnasingam et al., 2011 *(SCP)*	Total $n=893$ Treatment groups LPR $n=27$ LPR/GORD $n=66$	LNF (344) LTF (32) LAPF (584) Other (33)	Analogue symptom score: LPR:1.3 +/-3.1 LPR/GORD: 2.8 +/-3.7	Analogue symptom score: LPR: 1.8 +/-1.7, LPR/GORD 1.8 +/- 2.9 $p=0.018$	LPR 30% ($n=7$), LPR/GORD 62.3% ($n=38$)
Aiolfi et al., 2020 *(SR)*	Total $n=86$, 36 F Symptom Groups LPR $n=23$ LPR/GORD $n=63$	LTF	Median RSI LPR: 35.6 LPR/GORD: 37.9	Median RSI 1-year: LPR: 11.9, LPR/GORD: 12.8 2-year: LPR: 12.8, LPR/GORD: 11.8 3-year: LPR: 9.5, LPR/GORD 10.8	91% of total cohort at 2 years
Falk et al., 2020 *(SP)*	Total $n=90$, 63 F Symptom Groups LPR $n=23$ LPR/GORD $n=67$	LNF	Mean RSI LPR: 16, LPR/GORD: 20	Mean RSI LPR: 10, LPR/GORD: 12 Postop QoL improvement LPR/GOR: 80%, LPR 55%	12% in total cohort
Suzuki et al., 2022 *(SR)*	Total $n=8$ Symptom groups LPR diagnosed ON PPI $n=4$ LPR diagnosed OFF PPI $n=4$	LNF	RSI 19.6+/-4.9 RSI MII-pH OFF PPI Group 15.2+/-13.6 RSI MII-pH ON PPI Group 24.0+/-14.6	RSI 5.8 +/- 1.4 $p=0.008$ RSI MII-pH OFF PPI Group 4.8+/-2.1 ($p=0.125$) RSI MII-pH ON PPI Group 6.8+/-5.4 ($p=0.125$)	87.5% in LPR cohort

Table 2*abbreviations*: SP: Single-centre prospective, SCP: Single-centre controlled prospective, SR: Single-centre retrospective, SCC: Single-centre case-controlled study, RSI; Reflux Symptom Index, LNF: Laparoscopic Nissen Fundoplication, LTF: Laparoscopic Toupet Fundoplication, LAPF: laparoscopic anterior partial fundoplication, mths: months, wks: weeks, PPI: Proton Pump Inhibitor, QoL: Quality of life, MII-pH: multichannel intraluminal pH monitor

LPR Diagnosis and Management

Each of the five studies utilised LPR symptoms and laryngoscopy as part of their diagnostic workup. Primary LPR symptoms were reported by three studies and included hoarse voice, laryngitis, cough, globus pharyngeus, sinusitis. Suzuki et al. were the only ones that did not incorporate dual channel 24 h pH and Ratnasingam et al. the only ones that did not include EGD as a part of their workup. Aiolfi et al. and Suzuki et al. had additional investigations including GG and HMII and MII-pH and HMI respectively. Catania et al., Ratnasingam et al. and Suzuki et al. also compared signs and symptoms of LPR. Regarding operative intervention, Aiolfi et al. were the only group that did not utilise laparoscopic nissen fundoplication, instead managing their patients with a laparoscopic toupet fundoplication. Ratnasingam et al. also utilised a laparoscopic anterior partial fundoplication in a subset of patients.

Outcomes

The median follow-up ranged from 9 to 60 months. Four of the groups utilised RSI to assess the postoperative outcomes, whereas Ratnasingam et al. utilised the analogue symptom score. Catania et al. observed a statistically significant improvement of mean RSI from 31.5 ± 7.4 preoperatively to 10.5 ± 7.8 postoperatively ($p < 0.001$). Aiolfi et al. observed improvements from preoperative RSIs in the mid-30s to as low as 9.5 at 3 years post intervention. Suzuki et al. observed an improvement in the RSIs from 19.6 ± 4.9 to 5.8 ± 1.4 ($p = 0.008$) and Falk et al. from 16 to 10. Finally, the percentage of patients that were symptom free had a broad range from as low as 12% in Falk et al.'s cohort to 91% of the Aiolfi et al.'s total cohort at 2 years. In cohorts where percentage of symptom free patients were stratified by groups, the 'isolated LPR' cohorts showed lower totals symptom resolution rate compared to the combined 'LPR/GORD' cohorts although a meaningful meta-analysis could not be performed due to the heterogeneity of the data.

Discussion

The larynx is uniquely positioned between the gastro-intestinal and respiratory tracts and thus is exposed to a variety of chemical, immunological, mechanical and environmental stimuli that have led to several sensory adaptations that allow for rapid laryngopharyngeal control. In the setting of gastric refluxate reaching the larynx and hypopharynx, the rich supply of sensory neurons permeating the upper respiratory tract would manifest the pervasive symptoms of LPR even with low volume exposure [19]. Patients with LPR with suspected reflux are often also demonstrated to have high prevalence of oesophageal dysmotility compared to patients with GORD without concurrent LPR [20]. ARS aims to eliminate all types of reflux by reconstituting the mechanical and physiological barriers to reflux within the abdominal oesophago-gastric complex. ARS, in particular fundoplication, is well established as a highly effective treatment for typical GORD with efficacy reported between 85 and 90% [21–23]. The efficacy of ARS in the context of atypical reflux/LPR is however less clear with several recent systematic reviews reporting a wide range in success rates between 44 and 94% [5, 14].

With regard to efficacy of ARS, it is important to highlight the findings by Falk et al. [24] that patients with mixed LPR and concurrent typical reflux symptoms had substantially more benefit from ARS compared to patients with isolated LPR. In their cohort, total symptom resolution was rare. Falk and colleagues hypothesise that the significantly increased frequency of oesophageal dysmotility in the LPR group possibly explains the incomplete proximal symptom control. These findings were echoed by Ratnasingam et al. [25] who found patients with a combination of atypical throat symptoms (surrogate for LPR) and typical reflux symptoms had a good outcome following ARS comparable to patients with typical reflux and no suspected LPR. Specifically, Ratnasingam and colleagues noted that patients who did not have typical reflux complaints of heartburn and/or regurgitation had significantly diminished success. In the series by Catania and colleagues [26], 58% of patients with isolated LPR symptoms achieved normal RSI following laparoscopic Nissen fundoplication compared to 70% of the combined LPR/GORD phenotype. Indirect support for these findings that show better response from ARS to mixed LPR/typical reflux phenotypes are also present in the literature, where Kaufman et al.'s long term results from a series of 128 LPR patients with concurrent distal reflux disease reported reflux symptoms to have improved in over 90% of patients following fundoplication but cough/hoarseness (attributed to LPR) to have improved by only 65–75% [27]. Overall these studies suggest that careful patient selection and counselling of expectant outcomes are required by upper gastrointestinal surgeons when referred for ARS in this population.

The study by Suzuki et al. [28] is significant as it evaluated the role of ARS in two LPR patient groups: Patients without evidence of pathological GORD (RSI MII-pH OFF PPI Group) and patients with previously known pathological GORD but with no ongoing endoscopic evidence of GORD or abnormal distal oesophageal acid exposure (RSI MII-pH ON PPI Group). In both groups, all patients had either normal oesophageal mucosa or LA grade A oesophageal mucosal injury, a normal distal oesophageal acid exposure

profile and no symptomatic GORD events on MII-pH. In these distal-reflux 'negative' or 'silent' patients, LPR was diagnosed using Hypopharyngeal multichannel intraluminal impedance-pH (HMII) to demonstrate abnormal proximal acid exposure (APE). The HMII was performed using a specialised catheter with two pairs of impedance electrodes in the distal oesophagus, proximal oesophagus and the hypopharynx. APE was defined as either LPR ≥ 1/day and/or full column reflux events > 5/day. LPR was considered present, specifically on HMII when retrograde bolus transit occurred across all ring sets and reached the hypopharynx compared to FCR which was defined as reflux that reached the impedance 2 cm distal to the upper oesophageal sphincter, but did not reach the hypopharyngeal ring set. The 8 highly selected isolated LPR patients who underwent ARS reported significant symptomatic improvement to RSI scores (19.6 ± 4.9 pre-ARS to 5.8 ± 1.4 post-ARS, $P = 0.008$).

Whilst ARS may not provide a definitive cure for LPR, Catania and colleagues [26] argue that there is reasonable evidence to suggest that even reducing the volume of refluxate by 85–95% through ARS leads to significant quality of life improvement. In their study, a statistically significant improvement in disease-related quality of life improvement (through the LPR-Reflux-health-related quality of life score) was demonstrated. Voice symptom improvement was durable at 1, 6 12 and 24 month follow up. Similarly, Aiolfi et al. [29] demonstrated a reduction in RSI and LPR-HRQL scores as well as improvement to symptoms of hoarseness, chronic cough, throat clearing and odynophagia across both patients with isolated LPR symptoms and those complaining of both LPR and GORD. A durable 2- and 3-year improvement was also demonstrated despite loss of some of the cohort to the follow up period. Unlike most other groups, Aiolfi et al. used a partial fundoplication (Toupet) as their method of ARS. The inclusion of some patients with pH-impedance % AET ≥ 4.2 and DeMeester score > 14.72 within the isolated LPR symptom group confounds the results as the inclusion of this group of 'typical reflux' patients would likely have better RSI outcomes following ARS.

There is emerging evidence in the literature on the use of novel ARS techniques that may provide more consistent treatment outcomes in appropriately selected patients in the treatment of LPR. Magnetic Sphincter Augmentation (MSA) has been reported to provide improvement in patient reported symptoms of hoarseness, throat mucous, frequency of cough and RSI score in the 1-year data published by Ward et al. [30]. MSA has also demonstrated promising results in LPR patients with 'weakly acid/non-acid reflux,' defined as a reduced total acidic (pH < 4) and percentage time (< 4.2%) and an increased number of total reflux episodes (> 40) in the 24 h MII-pH, where improvement to LPR symptom related quality of life was demonstrated [31]. Recently, Sui et al. [32] reported on a retrospective case series of 183 patients with LPR treated endoscopic anti-reflux mucosectomy (ARMS) and demonstrated statistically significant improvements to postoperative RSI score, and symptom relief. This study however only included patients with concurrent acid reflux, which likely biases the results to demonstrate better outcomes, and did not include those with non-acidic/mix reflux or those patients without concurrent symptomatic reflux as is the focus on this review,

In examining the evidence for the role of ARS in LPR management several challenges arise. The lack of a universally practiced diagnostic criteria creates heterogenous study groups whose underlying parameters cannot be consistently compared. Use of 24-hour dual pH monitoring for diagnosis is not sufficient as LPR patient with non-acid reflux would not be accurately identified on pH based modalities [33]. The use of the more novel HMII needs to be balanced against the potential practical inaccuracies that arise from incorrect probe placement, and subsequent diagnoses. Given most recordings are taken over 24 h, the results of HMII may also be inconsistent with MII-pH. With respect to patient reported outcome measures, one study in our analysis did not use the widely adopted RSI for preoperative workup and postoperative assessment of efficacy, but rather analogue symptom scores [25]. A wide variety of ARS techniques were used in the included studies such as partial anterior, partial posterior, and posterior wrap fundoplication. Given each technique brings about variation in the degree to which the lower oesophageal sphincter is reconstituted, as well as subsequent side-effect profile [34], the most optimal surgical technique for LPR is also not clearly demonstrated.

This review has several limitations that should be considered prior to its applicability in an already challenging patient cohort. Most studies included for analyses had small patient cohorts with 2 studies having sample sizes of 8 and 12 patients with isolated LPR [28, 35]. Only the study by Suzuki et al. specifically assessed ARS in the context of isolate LPR whilst the other 5 studies included these patients as part of a subgroup within a larger population of LPR patients with or without underlying GORD. Two studies did not use RSI as the primary instrument to assess post-ARS symptom improvement or cure which limits the power of meta-analysis of the underlying data [25, 36]. The follow up period was also highly variable with Ratnasingam's study not clearly stating the number of patients lost to follow up which may have failed to capture patients with recurrent symptoms post ARS.

Conclusion

Our study identifies a lack of adequate information in the literature on the management of patients diagnosed with LPR but without underlying distal oesophageal reflux disease. Rather than the reliance on screening tests such as the RFS and acid reflux-based investigations such as 24-hour pH testing, a more considered approach using diagnostic modalities such as HMII is required for the correct dentification of this 'Isolated LPR.' Given that reflux-based LPR may be due to non-acidic reflux, such an approach would reduce the futile treatment of these patients with long term anti-acid therapies and self-select patients who are likely to respond to ARS. The current evidence for the utility of ARS is mixed with several studies suggesting that patients with mixed LPR/ typical GORD achieve a more predictable positive response from ARS compared to the isolated LPR phenotype. Further cohort studies with larger patient populations or a randomised controlled trial comparing ARS in both appropriately defined LPR patients with and without distal GORD are needed to provide more confident answer.

Key References

•• Falk GL, Gooley SC, Church NG, Rangiah DS. How effective is the control of laryngopharyngeal reflux symptoms by fundoplication? Symptom score analysis. European Surgery - Acta Chirurgica Austriaca. 2020;52 [3]:123-6.This article was significant because their case series was relatively large compared to other studies avaiable and specifically presented the outcomes between the 'isolated LPR' and LPR/GORD' subgroups and found patients with isolated LPR were less likely to have symptomatic improvement following surgery.

••Ratnasingam D, Irvine T, Thompson SK, Watson DI. Laparoscopic antireflux surgery in patients with throat symptoms: a word of caution. World J Surg. 2011;35 [2]:342-8. This study stratified patients into LPR (atypical throat symptoms) with and without reflux. Both groups of patients underwent standardised preoperative assessment. They reported poor outcomes in patients with isolated LPR symptoms following fundoplication and recommend ARS surgeons manage patient expectations when offering ARS in this patient cohort.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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