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Antireflux mucosal valvuloplasty versus proton pump inhibitors for the treatment of patients with gastro-oesophageal reflux disease in a tertiary healthcare centre in China: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Endoscopic antireflux therapy has shown promising potential in the treatment for gastro-oesophageal reflux disease (GERD). However, there is currently no universally accepted standard for endoscopic surgery. Therefore, we introduced antireflux mucosal valvuloplasty (ARMV), an innovative endoscopic treatment for GERD. We have conducted a cohort study to assess the association between ARMV and clinical outcomes, including risks and benefits. The objective of this trail is to compare the efficacy of ARMV with proton pump inhibitors (PPIs) therapy.

Methods and analysis 74 patients with chronic GERD will be randomised (1:1) to undergo either ARMV or continue PPI therapy. The primary endpoint is the GERD health-related quality of life score, measured 6 months postprocedure. Secondary endpoints include the GERD questionnaire score, presence of reflux oesophagitis, appearance of the mucosal flap, DeMeester score, PPI usage and the incidence of adverse events. After 6 months, crossover is allowed for the PPI group. Assessments will occur at baseline and at 3, 6, 12, 24 and 36 months postintervention.

Ethics and dissemination The study protocol has been approved by the Institutional Review Board of Qilu Hospital, Shandong University. Study results will be disseminated through peer-reviewed journals and presented at scientific conferences.

Trial registration number ClinicalTrials.gov (NCT 06348420).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ After the initial 6 months follow-up, participants in the PPI group have the option to undergo antireflux mucosal valvuloplasty (ARMV) surgery, offering flexibility by allowing them to switch treatments based on individual needs.
⇒ This study is one of the few randomised controlled trials comparing ARMV with proton pump inhibitor treatment, the primary pharmacological approach for gastro-oesophageal reflux disease.
⇒ While the randomised controlled design helps reduce bias, the influence of potential confounding factors cannot be entirely eliminated.
⇒ The long duration of the trial may compromise the participants' compliance.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD), as defined by the Montreal Consensus, is the pathological reflux of stomach contents into the oesophagus, leading to significant symptoms and complications. Affecting a substantial portion of the global population,[1] GERD commonly manifests as heartburn, regurgitation, belching and dysphagia. Complications include oesophagitis, strictures, Barrett's oesophagus and an increased risk of oesophageal cancer.[2] The condition not only imposes significant healthcare costs but also greatly diminishes patients' quality of life, requiring long-term management strategies given its rising global incidence.[3 4] Proton pump inhibitors (PPIs) are the first-line treatment for GERD, effectively reducing gastric acid secretion.[5 6] However, 25%–42% of patients fail to achieve full symptom relief with PPIs and prolonged use has been linked to adverse effects such as kidney disease, nutrient deficiencies and an elevated risk of infections,[7 8] driving the need for alternative therapies.

For patients unresponsive to PPIs, laparoscopic Nissen fundoplication (LNF), which wraps the stomach's fundus around the

oesophagus to reinforce the lower oesophageal sphincter (LES), is a commonly used surgical option.[9 10] Despite its potential for symptom relief, considerable uncertainty persists regarding the balance between its benefits and postoperative complications, such as dysphagia and gas bloat, highlighting the need for more randomised controlled trials (RCTs).[11 12] Additionally, magnetic sphincter augmentation, which places a ring of magnetic beads around the LES, has emerged as a promising alternative to LNF, offering technical ease and reduced hospital stay.[13 14] However, limitations such as MRI incompatibility and a lack of long-term outcome data remain.[4 15] Furthermore, innovative endoscopic treatments like radiofrequency antireflux therapy (Stretta) and transoral incisionless fundoplication provide less invasive alternatives. Although several trials support their safety and efficacy, concerns regarding their long-term effectiveness, high initial costs and technical complexity still pose challenges.[16–20]

Antireflux mucosal interventions, such as antireflux mucosectomy (ARMS) and antireflux mucosal ablation (ARMA), are minimally invasive techniques derived from advancements in endoscopic mucosal resection and submucosal dissection. These procedures use the natural process of mucosal scar formation to combat reflux.[21 22] Theoretically, scar contracture following ARMS narrows the gastro-oesophageal junction (GEJ), reinforcing the flap valve mechanism and thereby reducing reflux.[23] Current research, including multiple observational studies and early-phase clinical trials, has supported the feasibility, efficacy and safety of these techniques, presenting them as promising alternatives for GERD treatment.[24–28] However, although ARMS relies on scar formation, its broader clinical efficacy remains limited, highlighted by the absence of validation through RCTs.

Building on the foundational principles of ARMS, we developed an enhanced procedure called antireflux mucosal valvuloplasty (ARMV). This modified approach combines endoscopic mucosal resection with a novel double-layer mucosal flap, designed to strengthen the mechanical barrier against reflux. In our cohort study, ARMV demonstrated a 100% technical success rate and significantly reduced GERD symptom scores on standardised scales, with only minor and transient postoperative complications.[29] While this innovative approach theoretically offers additional benefits, it remains in the developmental phase and requires further clinical trials for technique refinement and comprehensive validation of its efficacy. To solidify ARMV's role in GERD management, ongoing research, including multicentre prospective studies and RCTs comparing ARMV to established therapies, is essential.

This paper presents a detailed study protocol designed to compare the efficacy and safety of ARMV with standard PPI therapy in the management of GERD.

Objective

The trial aims to evaluate the efficacy of ARMV in reducing GERD symptoms, assess postoperative complications and compare these outcomes with those of ongoing PPI therapy.

METHODS AND ANALYSIS

Study design

The trial is being conducted in the Department of Gastroenterology at Qilu Hospital, Shandong University. A total of 74 eligible participants will be enrolled and randomly assigned in a 1:1 ratio using a computer-generated sequence to ensure baseline comparability between the ARMV and PPI groups. The ARMV procedures are scheduled within 1 week of randomisation. After an initial 6 months follow-up, participants in the PPI group may choose to undergo ARMV surgery based on their preference, regardless of the follow-up results. Participants who undergo ARMV will be followed as a distinct cohort for an additional 36 months postprocedure. A comprehensive overview of the trial protocol is presented in figure 1. The trial began in March 2024 and is expected to be completed by December 2028. Recruitment commenced in September 2024.

Participants' eligibility

The study population consists of GERD patients who are controlled with PPI therapy but opt for an intervention over lifelong drug dependence. Patients are referred to gastroenterologists for GERD analysis and are selected to participate in the trial when they meet the study criteria. The inclusion criteria are 18–60 years of age, hiatal hernia ≤2 cm, sliding hernia≤2 cm, recurrence of GERD symptoms after cessation of PPIs, on daily PPIs for ≥1 year or twice daily PPIs for at least 8 weeks, oesophagitis grade B, C or D, Hill's flap valve grade≤III, observation of distal oesophageal pH<4 on at least 1–2 days within a 7 day period, with a percentage exceeding 5.3%, normal or reduced LES resting pressure (5–15 mmHg) at manometry, DeMeester score ≥14.7 or total reflux episodes exceeding 73 and signed informed consent. Patients with body mass index >35 kg/m^2, American Society of Anesthesiologists>2, Barrett's oesophagus, hiatal hernia >2 cm, oesophagitis grade A, Hill's flap valve grade >III, peptic ulcer disease, primary oesophageal motility disorders such as achalasia, severe gastroparesis, a previous antireflux procedure, uncontrolled systemic diseases, gastric outlet obstruction, portal hypertension or pregnancy are excluded from participation.

Recruitment process and informed consent

Gastroenterologists at Qilu Hospital, Shandong University, will recruit participants diagnosed with GERD from both outpatient clinics and inpatient wards. Recruitment details will be shared via leaflets for inpatients and announcements on hospital bulletin boards. Additionally, the recruitment campaign will use digital platforms,

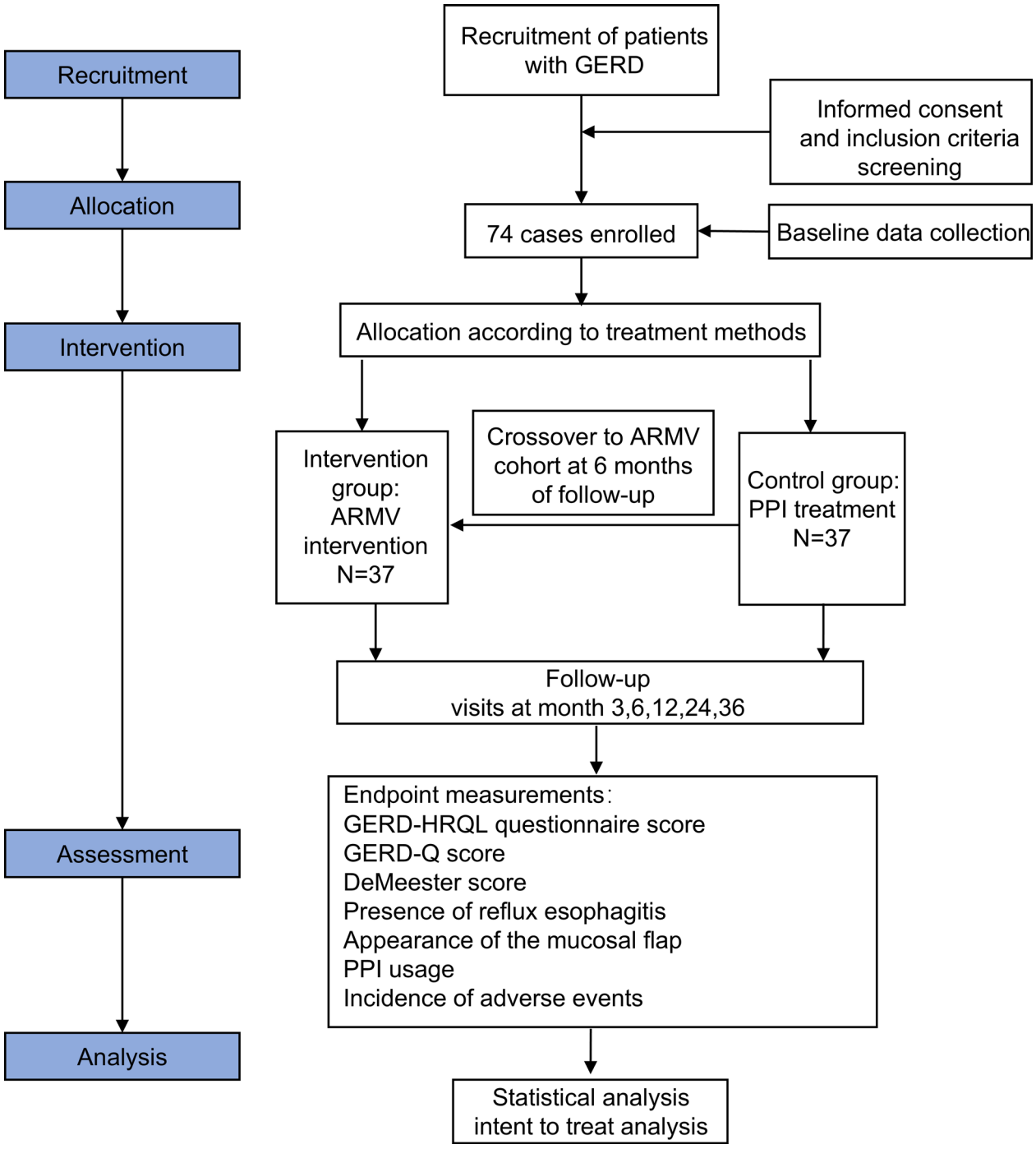

Figure 1 Trial flow chart. ARMV, antireflux mucosal valvuloplasty; GERD, gastro-oesophageal reflux disease; GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GERD-Q, gastro-oesophageal reflux disease questionnaire; PPI, proton pump inhibitor.

including the hospital's website and official WeChat accounts. Through these channels, interested patients or their family members can contact the project manager for more information, via either their attending physicians, phone or WeChat. After obtaining written informed consent, candidates will be evaluated by their attending physicians, who will document medical history, record symptoms and signs, collect imaging and endoscopic data and oversee their participation throughout the study. Participants will be given ample time to ask questions and consider their involvement before signing the study-specific consent form. See online supplemental material 1 for a copy of the participant consent form.

Randomisation

Authorised investigators will conduct the randomisation process after confirming that informed consent has been obtained and all inclusion criteria are met, with no exclusion criteria present. A computer-generated randomisation sequence will be used to assign each

eligible participant a unique randomisation number. The sequence will be concealed until the time of assignment, and allocation will be performed by a designated trial coordinator. The randomisation number, along with relevant participant data, will be recorded in a case report form to ensure the integrity and traceability of the randomisation process.

Blinding

Due to the distinct differences in interventions (ARMV vs PPI), blinding patients and surgeons is not feasible, which may introduce biases. Knowledge of the treatment can affect patient-reported outcomes like symptom relief, satisfaction and treatment adherence and may lead to placebo effects. Additionally, patient evaluations may be influenced by expectations rather than actual treatment effectiveness, potentially biasing the results, especially in subjective assessments. However, to preserve the objectivity of the trial outcomes, the trial protocol details will remain undisclosed to those collecting and assessing clinical outcomes, as well as to statisticians performing the data analyses. This approach will ensure a single-blinded design in which the outcome assessors and data analysts will be blinded, minimising bias in the evaluation of the results. Additionally, the use of objective endpoints and independent review of outcomes by blinded assessors will further support the reliability of the trial findings.

STUDY INTERVENTIONS

PPI (control group)

Patients randomised to the PPI group will adhere to the management scheme outlined in tables 1 and 2. PPI use will be recorded in medication diaries using generic names listed in table 1, along with daily dosage and frequency. If GERD symptoms remain well controlled with the current PPI dosage for at least 1 month, the regimen will be reduced by one step. If symptoms are poorly controlled, the dosage will be increased by one step according to the PPI algorithm, which aligns with good clinical practice.[30] The PPI management algorithm is outlined in detail in table 2.

Table 1 The utilisation of PPI

Generic name	Pill size (mg)	Brand names
Esomeprazole	20, 40	Nexium
Lansomeprazole	15, 30	Prevacid, Dakar, Lanso, Lanzor, Prezal, Lanzol
Omeprazole	10, 20, 40	Prilosec, Losec, Logastric
Pantoprazole	20, 40	Protonix, Zurcal, Pantozol, Zurcale
Rabeprazole	20	Aciphex, Pariet

PPI, proton pump inhibitor.

Table 2 PPI management algorithm

0.	None
1.	Half a single dose
2.	PPI (previous effective) at single dose
3.	PPI at double dose (b.i.d.) if symptoms are more severe than moderate despite 2 months' therapy at single dose
4.	Increase every 2 months by single dose to triple dose (2 q.a.m., 1 q.h.s.) and then quadruple dose (2 times per day)

Dosage will be categorised as 'double dose', ≥30 or 40 mg per day; 'full dose', 30 or 40 mg per day; 'half dose', 15 or 20 mg per day; 'occasional' or 'on demand', <'full dose' taken for <50% of days in the follow-up period. b.i.d., twice a day, q.a.m., in the morning, q.h.s., at bedtime.
PPI, proton pump inhibitor.

ARMV (intervention group)

Under general anaesthesia, patients are placed in the left lateral decubitus position and an endoscopic examination of the oesophagus and stomach is performed. The procedure uses a single-channel gastroscope (eg, 29-i10, Pentax, or GIF-H290T, Olympus) for its superior imaging and flexibility, along with a high-frequency generator (VIO300D, Erbe) for precise cautery control. A transparent cap (D-201, Olympus) is attached to the gastroscope to enhance visualisation and assist in manipulating the flap valve. The DualKnife (Olympus) is employed for its excellent manoeuvrability in the retroflexed position, allowing for precise dissection with minimal risk to surrounding tissues. In patients with oesophageal strictures obstructing scope passage, oesophageal dilation is performed using Savary–Gilliard dilators (Cook Medical) before ARMV, ensuring safe and unobstructed access.

During ARMV, a segment of mucosa at the GEJ is carefully dissected and reconstructed to form a mucosal flap, serving as an antireflux barrier. Cautery markings are placed on 75%–80% of the mucosal area along the lesser curvature, positioned about 2 cm below the dentate line to ensure precise flap formation and optimal antireflux function. After a submucosal injection of saline mixed with indigo carmine to delineate the dissection plane, the premarked mucosa is dissected caudally to cranially using endoscopic submucosal dissection techniques, minimising risk to adjacent structures. The cranial edge remains attached as an anchor, while the semifree mucosa naturally curls under itself, forming a robust double-layered flap. This manoeuvre, aided by mucosal tissue tension and careful dissection, strengthens the GEJ as an effective antireflux barrier. Metal clips are applied to anchor the free edge of the mucosa to the exposed submucosa and smooth muscle, ensuring the flap maintains its structure and function. Any visible bleeding is immediately coagulated with electric forceps to ensure haemostasis and minimise postoperative bleeding risk.

After the ARMV procedure, PPI therapy is continued for 1 month to promote mucosal healing. If symptoms

Table 3 Timing of endpoint measurements

		Time after treatment				
	Visit	1	2	3	4	5
Pretreatment	Month	3	6	12	24	36
Primary endpoint						
GERD-HRQL score	X		X			
Secondary endpoints						
GERD-Q score	X	X	X	X	X	X
DeMeester score	X		X		X	
Presence of reflux oesophagitis	X		X		X	
Appearance of the mucosal flap			X		X	
PPI usage	X	X	X	X	X	X
Incidence of adverse events		X	X	X	X	X

X means this time is required.
GERD-HRQL, gastro-oesophageal reflux disease health related quality of life; GERD-Q, gastro-oesophageal reflux disease questionnaire; PPI, proton pump inhibitor.

like heartburn or regurgitation recur, PPI therapy is resumed and all dosages and instances are recorded in a medication diary to track patient response and treatment efficacy.

Endpoints

The primary endpoint of this study is to assess the efficacy of ARMV compared with PPI therapy in reducing the GERD health-related quality of life (GERD-HRQL) score at 6 months.[31 32] The GERD-HRQL questionnaire evaluates both typical and atypical GERD symptoms, as well as patient satisfaction (online supplemental table 1). Secondary endpoints are GERD questionnaire (GERD-Q) score, DeMeester score, presence of reflux oesophagitis, appearance of the mucosal flap, PPI usage and the incidence of adverse events. The GERD-Q score is based on six key symptoms: heartburn, reflux, upper abdominal pain, nausea, use of over-the-counter heartburn medications and the frequency of symptom attacks within 1 week. The specific timings for the primary and secondary endpoint measurements are detailed in table 3.

Sample size calculation

The sample size estimation for this trial was based on detecting differences in GERD-HRQL score, informed by preliminary test results, clinical expertise and a review of relevant literature on similar interventions. To ensure the ability to detect meaningful differences between the groups, we used G*Power 3.1.9.2 software, conducting a two-tailed test with a power of 90% and a significance level of α=0.05. Participants will be randomised in a 1:1 ratio to either the ARMV (intervention group) or continued PPI therapy (control group). Based on existing data, we expect the mean GERD-HRQL score for the PPI group after 6 months to be 25.1±11.2 points, while for the ARMV group, we conservatively estimate a mean of 17.0±9.0 points, reflecting the greater efficacy anticipated from pilot studies.[29 33 34] These assumptions suggest an effect size of Cohen's d=0.80, which indicates a large clinical effect between the two groups. Accounting for a 10% dropout rate, the total sample size required is 74 participants (37 per group) to detect this effect size with 90% power. The sample size estimation was primarily conducted using G*Power 3.1.9.2 software and was further verified using two-sample t-tests in PASS 2021 software to ensure robustness.

Adverse events monitoring and reporting

The trial team will be responsible for monitoring, documenting and reporting all adverse events, including serious adverse events. As per the protocol, each adverse event will be thoroughly documented, detailing the event's nature, associated symptoms, time of onset and duration, response measures taken and final outcomes, such as resolution, remission or persistence. The team will also assess the potential relationship of the adverse event to the surgery or PPI treatment, considering any pre-existing conditions or concurrent medications. All adverse events will be promptly reported to the Institutional Research Ethics Review Committee, the medical monitor and the principal investigator.

Data collection, management and monitoring

Thorough data management and monitoring will ensure the trial's integrity and reliability. Patient records will be preserved, and trial forms were completed carefully with clear corrections. Dedicated personnel will organise the data for easy retrieval. Inspectors will ensure compliance with regulations and good clinical practice standards by verifying consistency between electronic records and original data. Any protocol deviations will be promptly documented and reported to the ethics committee. Additionally, the publication of articles or reports will require approval from the principal investigator, underscoring the commitment to transparency and quality in the dissemination of study results.

Follow-up assurance

We have secured sufficient funding from ZR2020QH184 and 2020M670044ZX to support the study's continuous operation throughout the 36 months follow-up period. Our research team, with extensive experience in managing long-term studies, has developed a comprehensive follow-up management plan, including strategies to track participants and minimise dropout rates. In addition, we will maintain regular contact with participants via WeChat and phone calls to facilitate data collection. Should unforeseen challenges arise, contingency plans are in place, along with a dedicated follow-up team, ensuring the successful completion of the study and the continuity of the follow-up process.

Missing data and adherence

Attrition bias may affect our results. To address this, we will compare and analyse the characteristics of participants

who complete the study with those who drop out, providing detailed reasons for data loss or withdrawal. We will assess whether participants with missing data differ from others and evaluate the potential impact on study outcomes. The reasons for withdrawal, loss to follow-up and missing data will be fully discussed in relation to the study's validity. To minimise bias from missing data, we will apply multiple imputation.[35] Additionally, all participants will be included in an intention-to-treat analysis and sensitivity analyses will assess the effects of non-adherence on outcomes.

Statistical analysis

The primary efficacy analysis will include all enrolled participants following the intention-to-treat principle. Missing follow-up data will be handled using the last observation carried forward method, while missing baseline values will be imputed using the overall mean. Continuous variables following a normal distribution, as verified by the Shapiro–Wilk test, will be summarised using mean values and SD. For non-normally distributed data, the median and range will be presented. Categorical data will be expressed as frequencies and percentages.

The primary endpoint will be the difference in GERD-HRQL score between baseline and 6 months postoperatively. Group comparisons between ARMV and PPI will be conducted using a 2×2 contingency table, with ORs and 95% CIs. Logistic regression analysis will follow, adjusting for baseline scores and eight potential confounders: sex, age, body mass index, baseline presence of hernia, Hill grade, oesophagitis grade, LES resting pressure and GERD symptom duration.

Secondary endpoints will be analysed using repeated measures analysis of variance and analysis of covariance. Linear regression will be employed to control for confounding variables, and mixed models will analyse repeated measures in the full ARMV cohort, including those who eventually cross over from the PPI group. All statistical analyses will be performed using SPSS (V.20.0; IBM, Armonk, NY, USA), with statistical significance set at $p<0.05$.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics and dissemination

This clinical trial has been approved by the Institutional Review Committee of Qilu Hospital, Shandong University (reference number: KYLL-202402-005-1) and is registered at ClinicalTrials.gov (NCT 06348420). The study will adhere to the principles outlined in the Helsinki Declaration, ensuring compliance with ethical standards and participant rights. All data collected during the trial will be shared with relevant investigators and the ethics supervision, audit and inspection committee throughout the research process. The auditing will be conducted by an independent team, separate from the investigators and the sponsor, to ensure objectivity and compliance with the study protocol. The study's outcomes will be disseminated through presentations at international conferences and publication in peer-reviewed scientific journals. Upon completion of the trial and the publication of the main manuscript, individual participant data will remain confidential, in compliance with the Data Security Law and the Personal Information Protection Law of the People's Republic of China. There are no publication restrictions related to this study.

DISCUSSION

GERD poses a significant clinical challenge due to its prevalence, impact on quality of life and potential complications. The traditional approach to GERD management includes pharmacological therapy with PPIs or surgical interventions like LNF. However, the limitations of long-term PPI use, along with the invasiveness of surgical options, have driven the search for alternative treatments. Therefore, we introduced ARMV, a minimally invasive endoscopic procedure for GERD treatment.

LNF, the most common surgical procedure for GERD, effectively strengthens the GEJ to prevent reflux.[36–38] However, its invasive nature often deters patients and providers seeking less burdensome options. Consequently, minimally invasive techniques, such as full-thickness plication and devices like Stretta, have been developed.[20] Clinical studies indicate that these alternatives are safe and effective in relieving GERD symptoms, improving quality of life, reducing oesophageal acid exposure and minimising reliance on PPIs.[39–41] Endoscopic treatments such as ARMS and ARMA, which involve removing mucosa at the gastric cardia to narrow the GEJ and promote scar formation, have also shown promise.[42–44] A meta-analysis of 15 studies involving 461 patients indicated that ARMS/ARMA are both viable options, improving subjective and objective outcomes in GERD management with a favourable safety profile.[45] However, long-term data and direct comparisons with traditional medications or surgeries remain scarce.

Our findings suggest that ARMV not only effectively controls GERD symptoms but also improves patient quality of life and reduces acid exposure. For instance, Inoue *et al* reported that, among 109 ARMS cases, only 61% showed minimal oesophageal changes and 19% exhibited Grade A oesophagitis.[46] In contrast, our study focused on Grade B/C patients and observed similar success rates despite the more complex nature of the surgeries. However, further studies are needed to confirm its applicability in broader clinical contexts. Interestingly, while traditional procedures like ARMS focus solely on scar contraction,[47 48] ARMV incorporates both scar contraction and mucosal flap formation, mimicking natural antireflux barriers. This novel approach yielded promising results in our cohort of 34 patients, leading to significant reductions in PPI use and

improvements in GERD-Q and GERD-HRQL scores. Although we encountered some complications, such as mucosal ulcers that persisted for 3 weeks post surgery, our strategy of administering a single dose of PPI for 1 month facilitated healing and minimised bleeding and perforation risks.

Given the limited exploration of endoscopic antireflux surgery, we designed a randomised, single-centre, controlled trial to evaluate the safety and efficacy of ARMV in alleviating GERD symptoms. This marks our first comparative study of ARMV, with PPI-treated patients serving as the control group. While PPIs are the first-line treatment for GERD, few RCTs have compared surgical options with standard PPI therapy.[30 33 34] Our approach is particularly beneficial for patients who are unwilling to continue long-term PPI use, intolerant to medications or experiencing adverse reactions. We chose not to compare ARMV with other antireflux surgical techniques, as further validation of the long-term efficacy and safety of various approaches is needed.

Despite these positive results, the study has certain limitations. The lack of blinding and single-centre design may introduce bias and limit the generalisability of the findings. Future studies should include multicentre trials with larger sample sizes to confirm our results and possibly refine treatment protocols for diverse populations. Additionally, longer follow-up periods are essential to evaluate the long-term outcomes of ARMV.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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