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REVIEW

Pre-operative clinical and instrumental factors as antireflux surgery outcome predictors

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Abstract

Gastroesophageal reflux disease (GERD) is nowadays a highly prevalent, chronic condition, with 10% to 30% of Western populations affected by weekly symptoms. Many patients with mild reflux symptoms are treated adequately with lifestyle modifications, dietary changes, and low-dose proton pump inhibitors (PPIs). For those with refractory GERD poorly controlled with daily PPIs, numerous treatment options exist. Fundoplication is currently the most commonly performed antireflux operation for management of GERD. Outcomes described in current literature following laparoscopic fundoplication indicate that it is highly effective for treatment of GERD; early clinical studies demonstrate relief of symptoms in approximately 85%-90% of patients. However it is still unclear which factors, clinical or instrumental, are able to predict a good outcome after surgery. Virtually all demographic, esophagogastric junction anatomic conditions, as well as instrumental (such as presence of esophagitis at endoscopy, or motility patterns determined by esophageal high resolution manometry or reflux patterns determined by means of pH/impedance-pH monitoring) and clinical features (such as typical or atypical symptoms presence) of patients undergoing laparoscopic fundoplication for GERD can be factors associated with symptomatic relief. With this in mind, we sought to review studies that identified the factors that predict outcome after laparoscopic total

fundoplication.

Key words: Gastroesophageal reflux disease; Antireflux surgery; Outcome predictors; Fundoplication; Nissen; Laparoscopy; High resolution manometry; Impedance-pH monitoring

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Core tip: Fundoplication is currently the most commonly performed antireflux operation for management of gastroesophageal reflux disease (GERD). Outcomes described in current literature following laparoscopic fundoplication indicate that it is highly effective for treatment of GERD. However it is still unclear which factors, clinical or instrumental, are able to predict a good outcome after surgery. Anatomical conditions seem to not be a risk factor for poor outcome. The predictability of success following laparoscopic fundoplication seems to be directly proportional to the degree of certainty that gastroesophageal reflux is the underlying cause of the patient's complaints. Thus, performing an accurate pre-operative clinical and instrumental evaluation is mandatory.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is currently a common condition; usually 10% to 30% of Western populations refer a weekly incidence of GERD symptoms. It has been recognized as a significant public health concern in the West[1,2]. Usually, the major part of patients with mild GERD are treated effectively with dietary and lifestyle changes, and/or low-dosage proton pump inhibitors (PPIs)[3]. For patients with GERD refractory to PPIs, different treatments can be started. In factantireflux surgery, and endoscopic procedures exist for patients who will to undergo an operative intervention. Fundoplication is currently considered the surgical gold standard for GERD treatment. Since its first description by Rudolph Nissen in 1956[4], the development of laparoscopy have increased the use of fundoplication worldwide. The indications for antireflux surgery in GERD patients were stated by the American Gastroenterological Association in 2013: It can be indicated in a GERD patient responsive, but not compliant to acid suppression therapy; in GERD patients who continue to experience troublesome symptoms despite an adequate pharmacological therapy; and in GERD patient who experience persistent extraesophageal symptoms despite adequate PPI therapy[5].

LF outcomes (as reported in current literature) point out that this technique is highly effective in GERD patients; the relief of symptoms is present in 85%-90% of subjects in the immediate post-operative period[6,7]. Despite these encouraging data, there can be complications that can necessitate a second intervention: Re-herniation, disruption or twisting of the fundoplication, persistent dysphagia or reflux-related symptoms, gas bloat syndrome, and esophageal motor disfunction[8,9]. Also, it is not clear the real incidence of redo antireflux surgery, because of small sample size or are single center studies. In the 90's, Lafullarde reported an overall reoperation rate of 10% after LF[10]. More recently, reoperation incidence is reported to be resembling 5%[11]. A systematic review performed on elective LF documented an overall reoperation incidence approximating 0.6%[12]. In the nationwide study from Denmark, an incidence near to 5% of redo antireflux surgery was reported in 2589 patients[13].

Being the increasing number of GERD patients without endoscopic esophagitis that are selected for LF, there is the need to highlight the great significance of a careful selection of patients who are likely to have a successful outcome after surgery. Virtually all demographic, esophagogastric junction anatomic conditions, as well as instrumental and clinical features of patients undergoing LF for GERD can be factors associated with a good outcome. With this in mind, we sought to review studies that identified the factors that could predict outcome after LF.

DEMOGRAPHICS FACTORS (GENDER, AGE, OBESITY, COMORBIDITIES)

Some studies revealed that gender can affect the clinical manifestation of GERD. Female gender with GERD showed at pH-monitoring a minor value of esophageal acid exposure and greater symptom scores than male gender cross-matched for grades of esophagitis[14,15]. In the same way, age seems to influence presentation, and GERD-related symptoms usually appear less severe in elderly, with a greater incidence of reflux complications[16]. In 2009, a study investigated the impact of gender and age on 5 years outcome of LF[17]. Authors showed that women were more likely to report a poorer outcome than men, describing heartburn, dysphagia and a lower satisfaction rate after surgery. Age, instead, did not prejudiced surgical outcome, even in presence of an higher incidence of complicated esophagitis and acid exposure in elderly than younger subjects[18]. These results were also confirmed by two large case series from Italy that compared antireflux surgical outcome in patients younger or older than 65 years[19,20]. Overweight and obesity are associated

with increased intraabdominal pressure, presence of hiatal hernia, increased frequency of transient sphincter relaxation , diminished lower esophageal sphincter (LES) pressure, and and impaired gastric emptying, thus increasing esophageal acid exposure time (AET) and total number of reflux (TNR), which have a clear role in GERD and promoting symptoms[21,22]. Recently, Luketina *et al*[23] retrospectively evaluated antireflux surgical outcomes in obese patients compared to normal weight GERD patients. Body mass index (BMI) was not associated to poorer outcome; reduction in GERD symptom score, GERD recurrence and reoperation rates were similar in both obese and normal weight patients. These data are consistent to several case-series[24,25], whereas only few studies reported poorer outcomes after LF in obese subjects, with increased intraoperative difficulties, risk of recurrence and re-herniation[26]. Finally, a study performed on a large cohort from North Carolina suggested that presence of pre-operative comorbities, such as diabetes, hypertension or pulmonary disease, were unlikely to impair the outcome of LF[27].

CLINICAL FACTORS: SYMPTOMS

Clinical presentation of GERD patients varies from typical to atypical symptoms, as well as extraesophageal symptoms and associated syndromes.

Heartburn and regurgitation are considered the hallmarks of reflux disease. Atypical reflux symptoms include non-cardiac chest pain and extraesophageal manifestations such as chronic cough, chronic asthma, chronic laryngitis, and dental erosions. Also, dyspepsia manifestations and irritable bowel syndrome symptoms can be present in up to 50% of GERD patients[28].

Many studies were performed to verify the post-operative symptomatic gain after LF, in order to estimate its clinical effectiveness. Morgenthal *et al*[29] studied a cohort of 166 subjects with 11 years follow-up of; authors showed that typical symptoms presence was a predictive factor for a long term good outcome after LF. Lundell *et al*[30] performed a systematic review about the outcome of antireflux surgery. They found that patients did not experience heartburn substantially in the year after LF but it reappeared over time, with a certain amount of patients reporting heartburn after 10 years. Similarly, patients reporting regurgitation reported a substantial reliefin the year after LF but with a recurrence 10 years after LF[30].

Achieving atypical GERD symptoms response is challenging: In a recent review, authors did not find any sure data on the efficacy of LF in relieving these manifestations, even if the majority of studies demonstrated some degree of improvement[31]. However, when a patient is selected on the basis of pH-impedance monitoring, LF showed a significant relief of extraesophageal symptoms but it seems to cannot improve all of the patients. Adaba *et al*[32] studied respiratory symptoms in patients with GERD and then treated with LF. They stratified the study population into three groups; patients with cough only, patients with cough plus other respiratory symptoms (asthma, COPD, bronchitis, interstitial lung disease and hoarseness of voice) and patients with other respiratory symptoms only. Patients with cough only were likely to have a better symptoms improvement than patients with cough plus respiratory symptoms and respiratory symptoms only in the short and long term, even if the small number of patients represented a limitation. This trend has also been observed in other studies[33,34]. Overall response rates were over 70% in the control of respiratory manifestations. A recent review speculated that cough and reflux may stimulate each other[35]. Cough showed the highest preoperative scores than all extraesophageal manifestations and was referred by about 45% of the subjects.

Finally, the presence of dyspepsia-like symptoms seems to be a negative factor for outcome. In fact, several studies reported that after surgery there are subjects who will get worse or exacerbate dyspepsia-like symptoms (epigastric fullness, bloating, abdominal pain, flatulence), with worsening in GERD symptom control in up to 50% at long term follow-up[36,37].

CLINICAL FACTORS: RESPONSE TO PPI

Acid-suppression with PPIs is the most widespread used therapy for GERD. Actually, patients who control their symptoms and resolve mucosal lesions with PPIs are referred to as "complete responders", whereas "partial responders" or "non-responders" are those increasingly numbers of patients experiencing only partial or no relief from reflux symptoms, even after optimized PPI[38]. The LF is currently contemplated in patients with hiatus hernia and, according to some surgeons, in patients non-responsive to PPI[39], whereas other surgeons do not consider the surgical treatment as a good option in PPI non-responders.

Several studies evaluated the clinical effectiveness of surgical treatment of GERD in PPI responders and nonresponders. According to Lundell *et al*[30], partial responders were the ones needing to use acid-suppressive medication and requiring surgical reintervention after LF. These results are consistent with a recent study; authors in fact showed that the pre-operative symptomatic response to PPI treatment was an excellent predictor of the subsequent response to LF[40]. In Campos *et al*[41] performed a multivariate analysis, demonstrating that pre-operative PPI refractoriness was a predictive factor of poor outcome after LF. In fact, PPI non-responders patients had a significantly effectiveness from the surgical treatment but it was still less successful when matched with PPI responders. Also, other studies considered the surgical outcome in non-responders, evaluating those also affected by atypical symptoms, reflecting that surgical procedure can be uneffective to treat atypical symptoms. Hamdy et coll, therefore, realized a prospective study on patients

responders and non-responders who underwent LF[42]. The two groups were matched for endoscopic grading of esophagitis as well as no significant difference between the two groups on functional assessment on esophageal manometric study of LES pressure and pH-monitoring. According to their findings, clinical outcome was better in PPIs responders regarding disappearance of heartburn and regurgitation, while there was no difference in improvement of dysphagia between both groups. Also, overall patient satisfaction with surgery was significantly higher in the good responders. Authors concluded that patients responder to PPI have a positive predictive factor for LF outcome, whereas PPI non responders are not at risk for a contraindication. However, PPI non-responders have experienced the failure of the pharmacological therapy, evaluating the surgical treatment as the last opportunity for their relief. So that, surgeons and gastroenterologists should accurately and carefully select patients non-responders to maximize LF outcomes: PPI non responders and/or patients complaining atypical digestive symptoms should avoid a surgical procedure to treat GERD, if the real presence of GERD and a possible symptom-reflux correlation is not documented.

ANATOMICAL FACTORS: HIATAL HERNIA PRESENCE

Mechanisms of GERD are multifactorial (dysfunction of esophageal peristalsis, gastric activity, and LES continence). The presence of hiatal hernia exposes patients to increased AET, TNR and to a more severe GERD pattern[43]. In literature in fact, is currently reported that at baseline hiatus hernia, LES resting pressure and length are significantly more compromised in patients with severe erosive reflux disease (ERD) and Barrett's esophagus (BE) compared to those with mild erosions and non erosive reflux disease (NERD).

Intuitively, GERD patients with a normal LES pressure at manometry would have less acid reflux and related symptoms at baseline; thus, they could be more likely to experience dysphagia after LF, with generally worse outcomes. On the other hand, hiatal hernia is often found in patients reporting dissatisfaction and/or undergoing reoperativeantireflux surgery. Its persistence after LF is in fact a predictive factor of negative outcome[44].

Lord *et al*[45] demonstrated not only that the grade of GERD well links with the functional and anatomical qualities of the gastroesophageal reflux barrier, with hiatus hernia, and that a defective LES is significantly more frequent in ERD or BE patients, but also that LF, which resolves the hernia and increases the LES pressure, offers in the same way good or excellent outcomes, irrespective of the presence of mucosal inflammation, and in all degrees of GERD[45]. Similarly, Lei *et al*[46] study the effect of LF in treating sliding hiatal hernia. They found that at 2 years follow-up in up to 93% of subjects a normal instrumental testing was present, with a good overall satisfaction. Cowgill *et al*[47] compared a group of patients with GERD that had a normal LES resting pressure, to a group of patients with inadequate LES, before and after LF was performed. They found that before surgery, patients with normal LES tone had symptom scores (for heartburn and regurgitation) similar to those patients with inadequate LES, and the symptom relief was also similar after LF. Inability to belch was not frequent at baseline, and its presence did not increased postoperatively. Furthermore, dysphagia scores significantly improved in patients, irrespective for inadequate and adequate LES pressure, whereas dysphagia frequency did not improve in those adequate or inadequate LES pressure at manometry.

ENDOSCOPIC FACTORS: ESOPHAGITIS, NERD AND BE

Deterioration of esophageal clearance function protracts contact of the refluxate, thus increasing mucosal damage, that can be documented during endoscopy. Therefore, GERD patients may present with a broad spectrum of endoscopic mucosal presentation (normal to esophagitis to BE).

However, a the majority of patients complaining GERD symptoms have no mucosal lesions at endoscopical imaging[48,49], while in others gastric acid reflux may trigger ERD and causing a weakening of esophageal peristalsis[50]. It could be expected that GERD patients without esophagitis suffer of a less symptomatic disease, and that the presence or absence of esophagitis at the endoscopic exam, could somehow influence the management of those patients, expecting that NERD patients could be treated with medical therapy whereas patients with esophagitis would need other approaches instead. Additionally, it could be thought that NERD subjects would have superior perioperative outcomes than ERD patients, but having less favorable long-term outcomes when compared to the ERDs.

Recently, there are confirmation that NERD subjects are similar to ERDs for reflux patterns, symptoms severity, and use of medical therapy[51].

Additionally, recent reports advocate that a less aggressive therapy (cisapride, anti-H2) in NERD subjects is often ineffective, and they necessitate high-dose PPI; also, they experience relapse frequently, and a lower response rates to omeprazole when compared to ERDs[52,53]. For these reasons, management strategies for NERD should be based on the same principles as those for ERD.

Lots of studies were taken to evaluate preoperative influence of esophagitis in GERD patients, and to evaluate how the presence of erosions would affect the outcome of surgery. The hypotheses that NERD patients would have better perioperative results with less

favorable long-term outcome than ERD is false. LF is an efficient treatment for GERD, with no significant clinical differences between patients with and without ERD at baseline. For patients with NERD, LF offers significant relief of symptoms and a marked diminution in the use of PPI[54].

Some investigators reported relatively poorer outcomes of LF for patients with BE and suggested the use of more aggressive surgical strategies for BE developed in GERD patients[55]. However, a study from Cowgill *et al*[56] compared patients with GERD with or without BE to verify the presence of differences in symptoms relative frequency and severity and in relative levels of acid reflux preoperatively and to verify symptom improvement postoperatively. Authors postulated that patients with BE would experience more severe reflux and symptoms at baseline, with poorer effects after LF than patients without BE. However, before surgery, even if BE patients showed higher DeMeester scores, symptom scores were not significantly different than patients without BE. After LF, symptoms scores improved for both group of patients. After LF, all symptoms scores significantly improved, whereas dysphagia frequency was higher in patients with BE. Similarly, Abbas *et al*[57] noticed that 67% of 49 BE patients after LF were asymptomatic at follow-up. Also, Oelschlager *et al*[58] reported excellent outcomes in GERD and BE patients, with up to 95% of the subjects reporting a persistent symptomatic improvement after LF. Tolone *et al*[59] showed optimal reflux control in BE patients after LF, documenting it by the means of MII-pH monitoring; also Authors showed regression of low grade dysplasia one year after surgery.

INSTRUMENTAL FEATURES: MOTILITY

Esophageal dysmotility commonly occurs with GERD. In the study by Savarino *et al*[60], which combined esophageal manometry and impedance, patients with reflux esophagitis have been shown to have a significant increase in esophageal motility and bolus transit abnormalities compared to healthy controls and patients with NERD. Although the association between GERD and esophageal dysmotility is clear, GERD symptoms relief after medical therapy is not proven to be helpful in improving esophageal motility. In fact, although PPIs are able to fully resolve reflux esophagitis and are successful in the majority of patients in terms of symptom relief, it has been shown that they have no effect on the improvement of esophageal body motility[61]. On the other hand, the surgical correction of GERD offers an improvement or a complete resolution of esophageal dysmotility[62]. However, medical good-sense purposes a limited role for LF if esophageal dysmotility is present, fearing for postoperative dysphagia development. Coherently, successful results after LF in patients with esophageal motor dysfunction are not easy to predict[63]. Various studies considered ineffective esophageal motility not to be a risk factor for prolonged postoperative dysphagia after LF[64,65]. Even if several studies reported excellent outcomes after LF in patients with manometric motor disorders, these results are not entirely shared. Dysphagia can observed in a considerable amount (up to 20%) of GERD patients and esophageal motor abnormalities after LF[66,67].

The study conducted from D'Alessio *et al*[68], showed that patients with esophageal motor dysfunction determined at manometry had adequate outcomes after LF if they were able to effectively clear a food bolus at preoperative esophagography. These patients had similar outcomes to those with normal esophageal motor function. Pizza *et al*[69], studied different patients divided into groups according to the motility pattern studied preoperatively with manometry. They divided a group A with impaired esophageal peristalsis, and group B without impaired peristalsis. Their study demonstrated that the two groups had a statistically significant improvement in symptom score and that preoperative defective esophageal peristalsis was not a contraindication to LF.

Another aspect to be considered is the preoperative LES resting pressure at manometry, because experience with LF in GERD patients and manometrically intact LES is limited. In the majority of GERD subjects an impaired LES competence is documented at esophageal manometry, thus reflux presence is easily argued. In those with manometrically adequate LES, several other mechanisms (transient involuntary relaxations of the LES, impaired esophageal peristalsis, decreased gastric emptying, increased intragastric or intraabdominal pressure, increased BMI, life-style habits) have been proposed to explain the occurrence of GERD.

Riedl *et al*[70] studied the importance of LES pressure and its hypothetic capacity to influence the outcome of LF when a normal pressure was present. In their study, they stratified 4 groups: Group Ⅰ (LES with a defective intra-abdominal length and a defective pressure), group Ⅱ (defective LES pressure), group Ⅲ (defective LES intra-abdominal length), and group Ⅳ (normal LES). They found no significant differences among the groups regarding the quality of GERD symptoms and quality of life scores. Similar conclusions led the study of Patti *et al*[71] where authors studied three groups based on the preoperative LES pressure. The resolution of symptoms and incidence in the novo dysphagia was similar among the three groups, irrespective of the preoperative LES status. Also, authors found that LF was linked to a higher percentage of postoperative dysphagia than partial fundoplication, regardless the LES pressure at baseline.

Finally, a new parameter at high resolution manometry, the esophagogastric junction contractile integral, was recently used to better prove the antireflux barrier efficacy of the junction[72]. The group from St Louis showed that this metric distinguished patients with normal AET from those with pathological values better than conventional LES parameters, and that it can be useful to evaluate the efficacy of the anti-reflux

surgery[73].

INSTRUMENTAL FEATURES: ESOPHAGEAL ACID EXPOSURE

Outstandingly, GERD patients are really a heterogeneous population. By means of 24-h ambulatory esophageal pH monitoring, AET can be quantified and qualified depending on the body position in which it appears. According this latter feature, three reflux patterns of acid reflux at pH-monitoring are usually reported: Unique upright, unique supine, and bipositional one. The presence of abnormal supine and bipositional AET are considered classic indication for antireflux surgery[74]. However, some investigators believe that symptom improvement and success after LF could depend upon the AET-body position pattern. It is reasonable to accept that LF outcomes can vary according to the reflux patterns. Upright reflux, for example, is cogitated to be a less severe GERD pattern, whereas bipositional reflux seems to be associated with advanced, severe disease. Although upright reflux is considered an initial form of GERD, these subjects are supposed to present a greater incidence of aerophagia and dyspepsia. Also, these patients are supposed to have worse postoperative outcomes after LF, including higher rates of postoperative gas bloating and flatus, when compared to those with supine or bipositional pathological AET[75,76]. Consequently, some physicians have been hesitant to indicate LF in presence of isolated upright pathological AET[77].

However, several papers are even in contrast on this matter. In fact, different studies found a similar symptoms relief in patients with pathological upright reflux and in those with pathological supine or bipositional AET[78,79]. Only two studies evaluated objectively the outcomes of LF and demonstrated that isolated upright reflux patients had a good outcome after surgical intervention[80,81]. Other authors have recently reopened the debate and it has been reported that poorer symptomaticimprovement occurs after surgery in patients with pathological upright reflux[82]. Cowgill *et al*[83] studied a large cohort of GERD patients who required antireflux surgery. Authors stratified patients according to positional AET features at baseline pH-monitoring. Patient with reflux occurring in any position, even in only upright reflux, experienced similar good symptom improvement after LF; in fact, a larger percentage of patients with upright reflux defined their overall outcomes as "excellent" or "good". All symptoms improved postoperatively. Authors concluded that after LF, symptoms of GERD improved in all reflux patterns and that LF dramatically improves GERD symptoms, irrespectively of the reflux pattern; thus, antireflux surgery is encouraged. Actually, it remains debated whether upright reflux should be considered as a relative contraindication for LF, because studies comparing long-term objective and subjective parameters are lacking.

INSTRUMENTAL FEATURES: IMPEDANCE-PH MONITORING

Combined multichannel intraluminal impedance-pH (MII–pH) monitoring can identify reflux events independently of its pH quality. In recent years, in fact, MII-pH monitoring has become a progressively adopted method in the evaluation of GERD. Because MII-pH monitoring detects retrograde movements in the esophagus regardless of an acid pH drop, it permits to document either nonacid or weakly acidic reflux events (with a pH higher than 4). This central advantage allows to evaluate GERD patients with refractory symptoms during acid-suppression therapy; in fact, recent studies have shown the capacity of MII-pH monitoring in increasing the symptom index sensitivity for patients on PPIs[84,85].

Mainie *et al*[86] assessed LF as a management for patients with PPI refractory symptoms associated with reflux, by means of MII-pH monitoring. Authors found that at baseline 18 of 19 patients had a positive symptom index and one, a negative symptom index. At postoperative follow-up (14 mo), 94% of patients with a positive symptom index were asymptomatic or with a marked improvement. Persistent symptoms were experienced in the patient with a negative symptom index, and one patient had recurrent symptoms after 9 mo. Authors concluded that patients resistant to PPI with a positive symptom index demonstrated by MII-pH monitoring could be managed successfully by LF.

Del Genio *et al*[87] in 2008 verified if the MII-pH was effective to provide a correct selection of patients for LF. Authors prospectively assessed and reviewed data from 314 consecutive patients not responsive or not compliant to PPI who underwent MII-pH for GERD. One hundred fifty-three patients who underwent LF with a minimum follow-up of 1 year were included in the study. Outcomes were reported for patients with normal and ineffective peristalsis and for patients with positive pH-monitoring, negative pH-monitoring and positive total number of reflux episodes at MII, and negative pH-monitoring and normal number of reflux episodes at MII and a positive symptom index correlation with MII (hypersensitive esophagus patients). The overall patient satisfaction rate after surgery was 98.3%. No differences in patients' satisfaction and clinical postoperative symptom score were recorded between the groups as stratified by MII-pH. Authors concluded that MII-pH provided a useful objective selection of patients for LF and that LF can provide excellent outcomes in either patients with positive pH or negative pH and positive MII monitoring or symptom index association. These results were later confirmed by another Italian group that documented the positive impact of LF on reflux control in patients who

underwent MII-pH before and after surgery[88].

CONCLUSION

The LF is a good and efficacy therapeutical option for GERD. However, due to great heterogeneity in the phenotypical appearance of GERD, it is arguable that the outcomes of LF can be affected by a great number of factors. Based on the results highlighted in literature, a correctly fashioned LF, and, more important, a correctly indication to LF can provide optimal results with good patient satisfaction. Thus, in large part, the predictability of success following LF is directly proportional to the level of certainty that GERD is the underlying cause of the patient's symptoms. Pre-operative testing are mandatory, especially MII-pH, due to its ability to better stratify GERD patients and to better identify the reflux-symptom association.

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