Best predictors for a good outcome after laparoscopic fundoplication in patients with gastro-oesophageal reflux disease

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Thesis Abstract

The Lyon consensus 2.0 states that the actionable definition of gastro-oesophageal reflux disease requires conclusive evidence of reflux-related pathology on endoscopy and/or abnormal reflux monitoring in the presence of compatible troublesome symptoms (Gyawali et al., 2023). Gastro-oesophageal reflux disease or reflux disease has heterogeneous manifestations, and the symptoms range from typical, as in heartburn and regurgitation, to atypical, including chronic cough, hoarseness, asthma, laryngitis, dental erosions, and ear-nose-throat complaints. Whilst treatment of reflux disease is usually initiated with anti-reflux medications and life-style modifications, about 40% of patients (Kahrilas et al., 2013a, Sigterman et al., 2013, Sifrim and Zerbib, 2012, Savarino et al., 2017, El-Serag et al., 2010) either do not respond or show discontent with first-line treatment.

Laparoscopic fundoplication, first described in 1991, has replaced conventional open fundoplication, and is considered the gold standard surgical treatment for reflux disease. The technique involves mobilising the gastro-oesophageal junction to reposition the lower oesophagus below the diaphragm, suturing the diaphragmatic crura to repair the hiatal defect, and creating a new valve to prevent reflux of gastric contents into the oesophagus. Laparoscopic fundoplication is an effective surgery for gastro-oesophageal reflux disease and has a success rate of 80-85% in the long-term. However, the exact cause for the failure of this small, but significant 15-20% subset is not clear, even after three decades since the introduction of fundoplication. The conundrum of whether there is a single factor, or a combination of factors, that leads to recurrence of symptoms is not clearly understood.

The aim of this Master of Surgery thesis is to evaluate and identify the predictive value of preoperative factors to:

- Improve post-operative outcomes after laparoscopic fundoplication to close to a 100% satisfaction rate.

- To avoid laparoscopic fundoplication in gastro-oesophageal reflux disease patients who are doomed to fail.

This research aims to identify predictors of success prior to laparoscopic fundoplication to help the surgeon to avoid operating on patients who will not benefit from the operation. This thesis presents a narrative review of the current literature, followed by a systematic review using predictors

identified in the narrative review to assess outcomes after laparoscopic fundoplication. This research tested data held in our institutional database for patients who have undergone laparoscopic fundoplication against the outcomes to validate the predictors against the same outcomes.

Through the narrative review, predictors such as male sex, typical symptoms, response to anti-reflux medication, and an abnormal preoperative pH study were found to be associated with excellent outcomes after fundoplication. Age, weight, grade of oesophagitis, oesophageal peristaltic function, and reflux patterns did not seem to affect outcomes. However, female sex, depression, atypical symptoms, long-segment Barrett's oesophagus, morbid obesity, and delayed gastric emptying were some of the potential predictors needing further study. Elderly patients with reflux disease, patients with equivocal or negative pH studies, and pre-operative dysphagia with a hypertensive lower oesophageal sphincter were identified as pre-operative predictors requiring careful consideration. The role for delayed gastric emptying effects on fundoplication outcome was not clearly established.

Reviews included in the thesis identified the heterogeneous nature of the outcomes reported in each study. A meta-analysis was hence not possible. Although objective outcomes included endoscopy, pH study, and manometry findings to assess the integrity of lower oesophageal sphincter, the statistical methods to derive results were varied. Subjective outcomes usually assessed individual symptoms including heartburn, dysphagia, regurgitation and assessed them as symptom scores, satisfaction scores, LIKERT scales or visual analogue scales. Through extensive research based on narrative, systematic and, subsequently, database validation, it is recommended that all future studies should have at minimum the following: standardised subjective and/or objective outcomes, minimum duration of follow-up, clear definition of failed fundoplication, and similar analytical methods of statistics when reporting the results of outcomes.

The rate of successful outcomes after laparoscopic fundoplication has remained consistent at 80-90%. While the widespread principles in the technique of laparoscopic fundoplication have remained unchanged except for a few modifications in the wrap techniques (partial fundoplication for females and manometric findings of inefficient distal oesophageal peristalsis), the long-term failure rate of 10-15% has not improved.

While the demographic and pre-operative clinical factors for gastro-oesophageal reflux disease have undergone extensive investigation and thorough analysis in scientific literature, outcomes related to predictors like reflux patterns and delayed gastric emptying remain elusive and- under-researched.

Pre-operative factors play a significant role in determining the outcomes after laparoscopic fundoplication for gastro-oesophageal reflux disease. Based on literature review and systematic review, followed by our institutional based database study, there is evidence of specific predictors that should be selected carefully, even with objective confirmation of gastro-oesophageal reflux disease.

Female sex, poor or ineffective oesophageal peristalsis, and percentage of time pH <4 were identified as predictors that affect the outcome of anti-reflux surgery. Gastric emptying time and reflux patterns (based on pH studies) were found to be under-researched regarding their effect on outcomes. Whereas reflux symptoms, regurgitation, body mass index, grades of oesophagitis, non-dysplastic Barrett's oesophagus, status of lower oesophageal sphincter on manometry did not affect the outcomes after fundoplication. Age as a factor remained equivocal and further large randomised controlled studies will help establish its effect on outcome.

The work included in this Master of Surgery thesis has contributed to greater understanding of the pre-operative factors associated with success or failure after laparoscopic fundoplication.

What do we understand?

1. Though the pre-operative work up for gastro-oesophageal reflux disease (GORD) patient requires investigation to confirm reflux disease (e.g. ambulatory 24hr pH study), careful selection of patients is imperative.
2. Patients with high-risk predictors including female sex, comorbidities including depression, delayed gastric emptying, low percentage of oesophageal peristalsis, and long segment Barrett's oesophagus should be routinely counselled pre-operatively. The expectations from surgery should be clearly discussed and established pre-operatively.
3. Standardising subjective outcomes in future studies and implementing them in clinical practice will help streamline further research work and improve engagement of patients for long term follow up for at least 5 years.
4. Current predictors in literature have been extensively investigated and there is a need to study comorbidities associated with GORD like diabetes mellitus, obstructive sleep apnoea, irritable bowel syndrome and smoking.

Proposed future work needed on this topic is outlined in the concluding chapter.

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Declaration

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Dr Rippan Shukla, October 2024

Published Work

Choosing the right patient for laparoscopic fundoplication: a narrative review of preoperative predictors

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Application of machine learning models to identify predictors of good outcome after laparoscopic fundoplication

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1. Introduction

1.1 Gastro-oesophageal reflux disease

1.1.1 Definition

Gastro-oesophageal reflux disease is defined by the Montreal consensus as a condition that develops when the reflux of gastric contents into the oesophagus causes troublesome symptoms or complications (Vakil et al., 2006). The Montreal definition is straightforward and uncomplicated and does not incorporate other elements that interplay with reflux disease to make it more complex and heterogeneous. However, a study by Dent et al and Moayeddi et al. found low sensitivity and specificity of gastro-oesophageal reflux disease symptoms compared to objectively confirmed disease (Moayyedi and Talley, 2006). The Lyon consensus 2.0, conversely, states that the actionable definition of gastro-oesophageal reflux disease requires conclusive evidence of reflux-related pathology on endoscopy and/or abnormal reflux monitoring in the presence of compatible troublesome symptoms (Gyawali et al., 2023). The consensus emphasises on reflux symptom that has high or low probability and correlation with objective evidence of reflux disease. Compared to the original Lyon consensus 1.0 REF missing, the new criteria include changes made to objective endoscopic findings of gastro-oesophageal reflux disease, use of wireless pH monitoring and use of pH studies on or off proton pump inhibitor therapy.

1.1.2 Pathophysiology of gastro-oesophageal reflux disease

Gastro-oesophageal reflux is a multifactorial disease. Typically, the gastro-oesophageal junction barrier loses its efficacy, causing influx of gastric contents (both acidic and non-acidic) into the distal (and sometimes proximal) oesophagus causing oesophageal and extra-oesophageal symptoms. One or more of the following factors are compromised to cause gastro-oesophageal reflux disease:

1.1.3 Anti-reflux barrier and transient lower oesophageal sphincter relaxations (TLOSRs)

The most common cause in the pathophysiology of gastro-oesophageal reflux disease is incompetence of the gastro-oesophageal junction (GOJ) barrier. This anti-reflux barrier incorporates a high-pressure zone made up of the lower oesophageal sphincter, a 3 – 4 cm region of circular muscle in the distal oesophagus. This zone is attached to the diaphragmatic crura via the phreno-oesophageal ligament. Normally, there is physiological relaxation of the competent lower oesophageal sphincter and

diaphragmatic crura to allow venting of gas from the stomach, an event called transient lower oesophageal sphincter relaxations (TLOSRs) (Figure 1.1). Reflux disease can result if the transient relaxations, which occur independent of swallowing, become prolonged and frequent in an anatomically stationed lower oesophageal sphincter(Mikami and Murayama, 2015). With the development of a hiatus hernia (discussed in 1.2.4), a low-pressure zone/hypotonic lower oesophageal sphincter can also occur (Pandolfino et al., 2010) compounding the problem. Finally, the angle of His, also called the oesophago-gastric angle, located on the patient's left between the oesophagus and fundus of the stomach, can be disrupted, contributing to reflux disease (Figure 1.2) (Andrews WG, 2021).

1.1.4 Impaired oesophageal clearance

Some reflux of gastric contents into the distal oesophagus is physiological to a certain extent. Oesophageal clearance depends on the coherence of its worm-like peristalsis. Absent, ineffective, or fragmented peristalsis can lead to inadequate neutralisation of acid from reduced salivary transport to the oesophageal mucosa, increased reflux burden, and impaired clearance(Reddy et al., 2017). The more progressive form of reflux disease has a significantly lower percentage of complete bolus transit in addition to excessive reflux events, than those diagnosed early in the phase of gastro-oesophageal reflux disease(Savarino et al., 2011). This explains why reflux disease is more severe inpatients with Barrett's oesophagus and those with erosive reflux disease who have little or no symptoms at presentation.

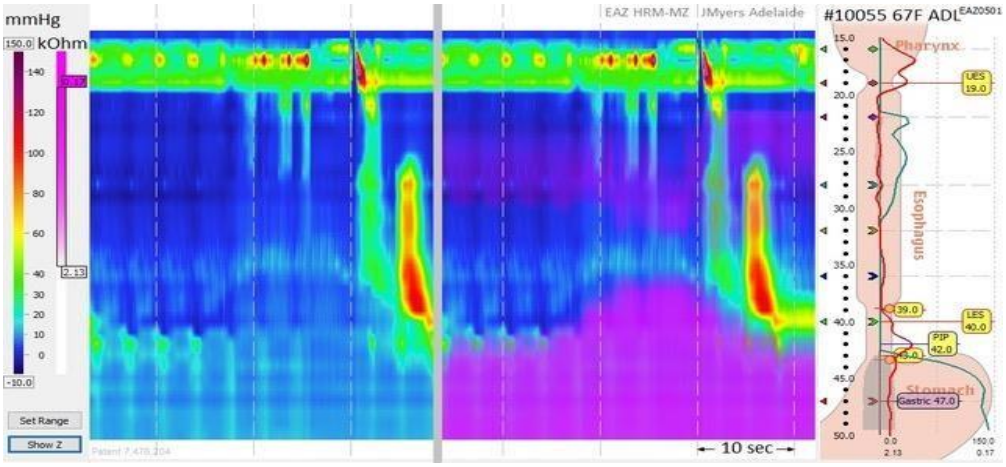


Figure 1-1: A TLOSR with reflux episode. First, there is inhibition of the crural diaphragm, the LOS relaxes, and this is accompanied by a gastro-oesophageal reflux. (Image supplied and used with permission courtesy of Dr Jennifer Myers, Oesophageal Function, University of Adelaide).

1.1.5 Epithelial Tissue Resistance

The integrity of oesophageal mucosa is maintained by cell-to-cell junctions which prevent the infiltration of toxic substances(Kahrilas et al., 2013b). Biopsies in patients with erosive and non-erosive reflux disease show evidence of microscopic oesophagitis: necrosis, erosions, eosinophilic or neutrophilic infiltrate, basal cell hyperplasia, elongation of papillae, or dilation of intercellular spaces(Pandolfino and Shah, 2006). Therefore, reduced mucosal integrity is a potential mechanism of gastro-oesophageal reflux disease. Mucosal impedance is an emerging field of study to examine electrical conductivity and mucosal integrity of the oesophagus. A lower baseline mucosal impedance is associated with increased acid exposure and dilated intracellular spaces and may differentiate patients with objective gastro-oesophageal reflux disease from other disease states(Mittal, 2013, Kahrilas et al., 1999).

1.1.6 Hiatus Hernia

The exact mechanism for the cause of hiatus hernia is unknown, but loss of elasticity with resultant weakness of the phreno-oesophageal ligament and shortening of the oesophagus are potential factors.

Hiatus hernia leads to complete disruption of the anti-reflux mechanism, exacerbating gastro-oesophageal reflux disease(Gordon et al., 2004). There are four types of hiatus hernia (Figure 1.3).

Type I or sliding hiatus hernia is the most common type of hiatus hernia and accounts for 90% of cases. The gastro-oesophageal junction is pulled proximally in the cranial direction due to weakness in phreno-oesophageal ligament, causing an acid pocket(Boeckxstaens, 2007). This exposes the oesophageal epithelium to reflux at times of lower oesophageal sphincter relaxation, even whilst swallowing or during secondary peristalsis(Kahrilas et al., 2013a).

Type II hernia results from a localised defect in the phreno-oesophageal ligament so that the gastro-oesophageal junction remains normally fixed, whereas the gastric fundus forms the leading part of the hiatus hernia.

Type III are mixed type I and type II hiatus hernia wherein there is herniation of cardia and fundus of the stomach, along with sliding of the gastro-oesophageal junction proximally.

Type IV para-oesophageal hiatus hernia are due to a large defect or widening of the hiatus with an elongated phreno-oesophageal ligament resulting in herniation of other organs, usually colon, along with the stomach.

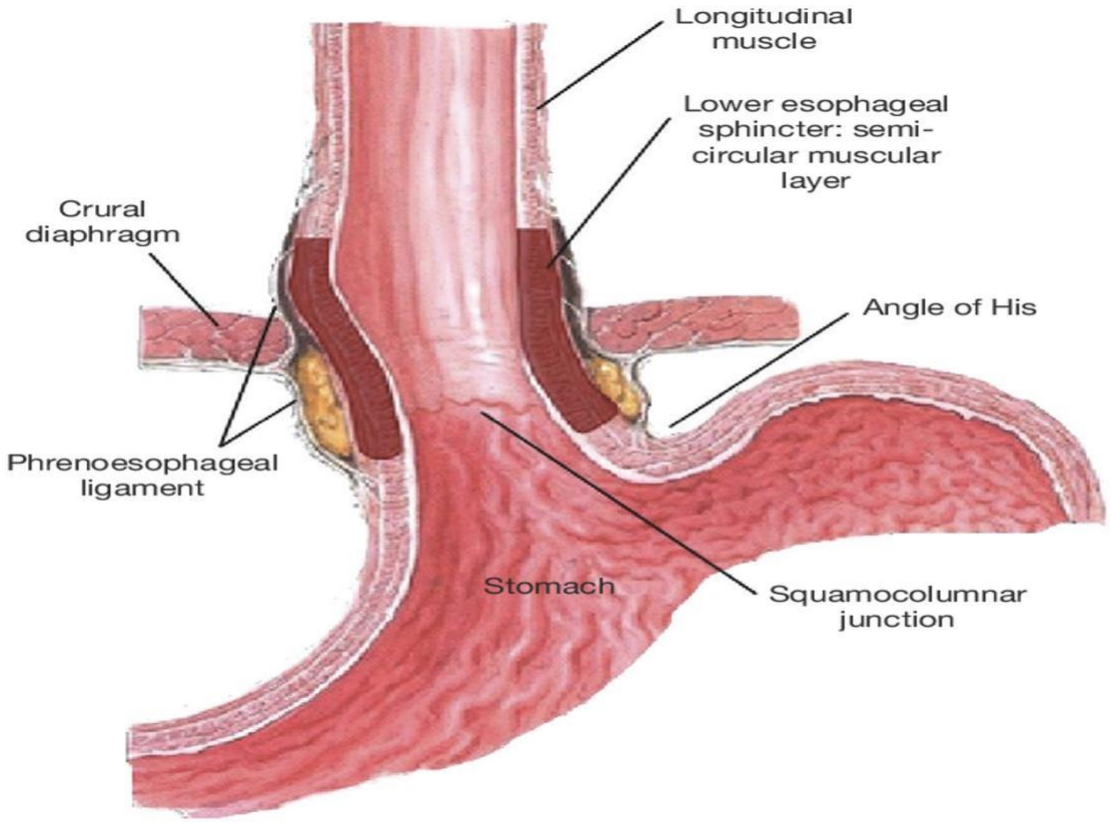


Figure 1-2: Normal anatomy of gastro-oesophageal junction with anti-reflux mechanism; depicting the Diaphragm, Angle of His, Intra-abdominal portion of oesophagus, Lower oesophageal sphincter, and Phreno-oesophageal ligament (Reproduced from: Weston G. Andrews, Brian E. Louie, Ann Laparoscopic Endoscopy Surg (2021) DOI: 10.21037/ales.2020.04.01, Open Access, AME Publishing Company, by the Creative Commons BY-NC-ND 4.0 license.)

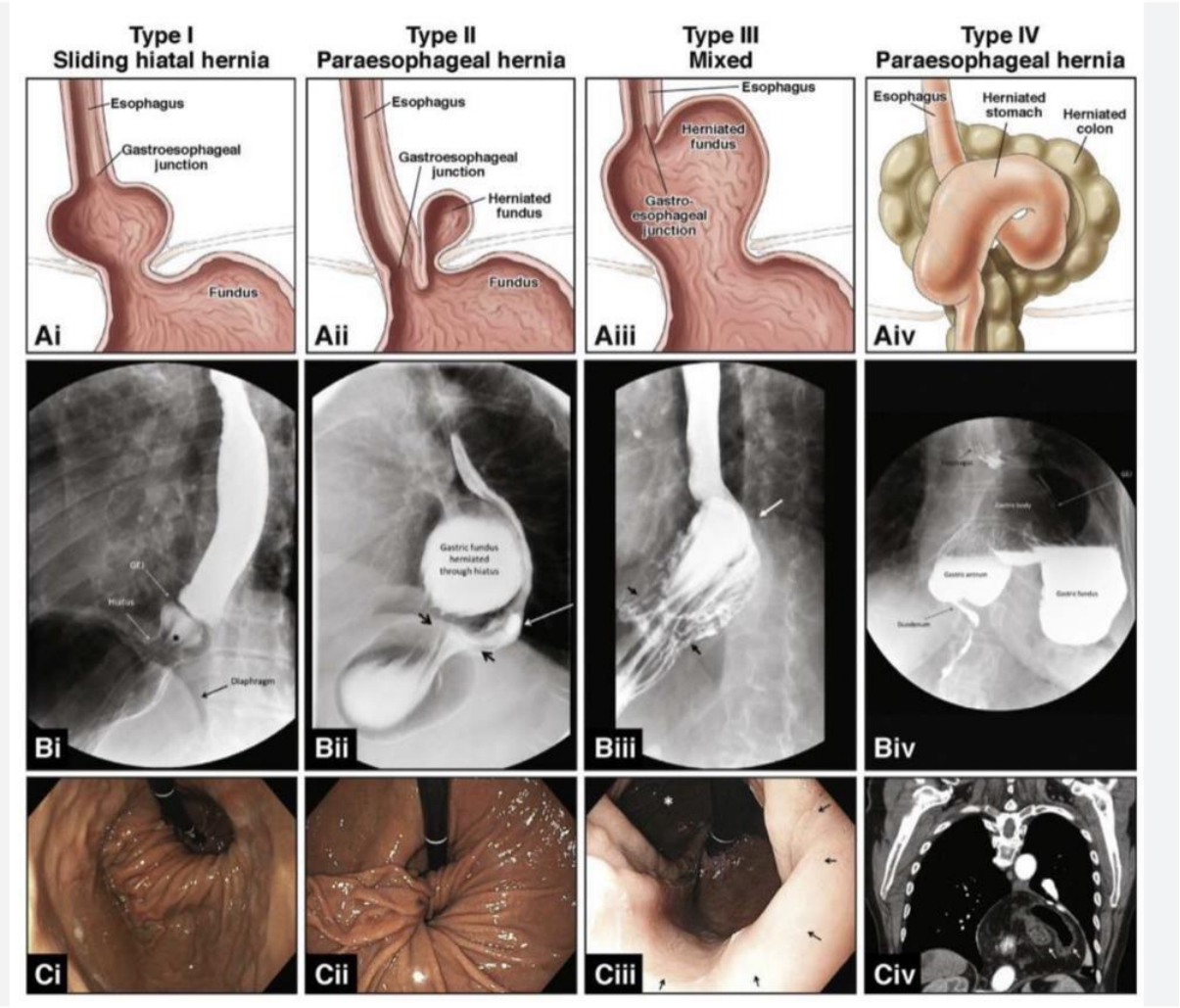


Figure 1-3: Types of Hiatal hernia; Type 1 is a sliding hiatus hernia; Type 2 is a para -oesophageal hiatus hernia; Type 3 is a combination of a sliding and para-oesophageal hernia (mixed); and Type 4, a mixed hiatus hernia, incorporating other organs along . Reproduced with permission from Callaway JP, Vaezi MF, Here and Now: Clinical practice Hiatal and Paraesophageal Hernias, Clinical Gastroenterology and Hepatology, 2018, doi: 10.1016/ j.cgh.2017.12.045 (Callaway and Vaezi, 2018)

1.2 Epidemiology and Prevalence

Gastro-oesophageal reflux is a common, chronic, debilitating disease resulting in millions of dollars in healthcare costs and loss of productivity world-wide(Mason and Hungin, 2005).

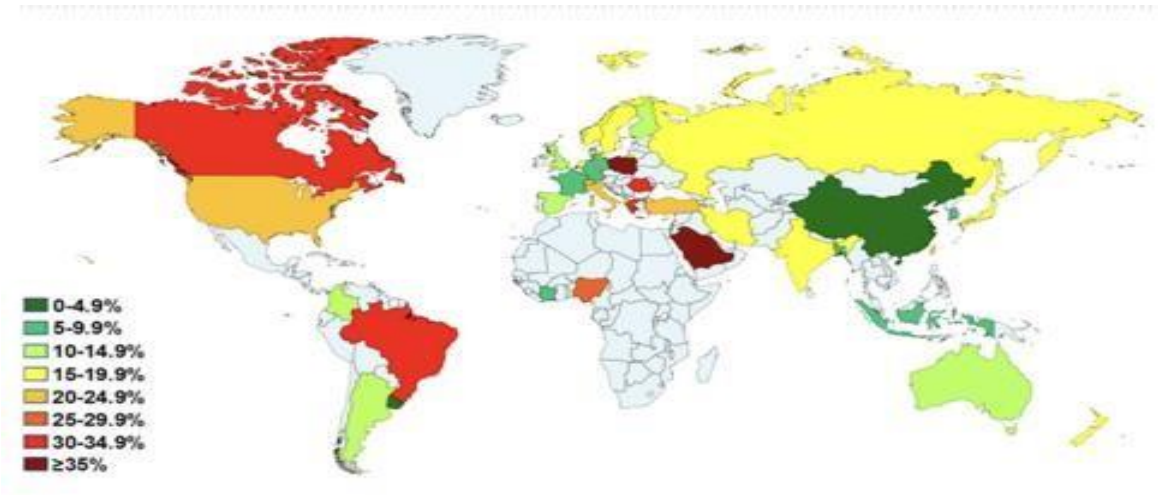


*Figure 1-4: Distribution of Gastro-oesophageal reflux disease prevalence in the world, reproduced with permission from Reproduced with permission from Nirwan, J.S., Hasan, S.S., Babar, ZUD. et al. Global Prevalence and Risk Factors of Gastro-oesophageal Reflux Disease (GORD): Systematic Review with Meta-analysis. Sci Rep **10**, 5814 (2020). https://doi.org/10.1038/s41598-020-62795-1 (Nirwan et al., 2020)*

According to a review by Nirwan et al, 2020, gastro-oesophageal reflux disease has a global prevalence of 13.98% with significant variations between regions and countries. Whilst the prevalence of gastro-oesophageal reflux disease in Australia and UK is 10-14.9%, the prevalence in USA is 20-24.9%. In the past, reflux disease was considered a disease which affected the middle aged and elderly age group. However, over the last decade, there has been a significant increase in the proportion of younger patients with reflux disease, especially those within the age range of 30-39 years(Nirwan et al., 2020). Females are at a slightly higher risk of reflux disease compared to males. The difference in reflux symptoms affecting women more than men is likely due to the loss of anti-inflammatory effect of oestrogen post menopause. The other postulation is lower pain threshold and increased pain sensitivity in women compared to men(Chen et al., 2011). Other factors like comorbid psychological factors, including anxiety and depression, which are known to be more common in women compared

to men, may in fact worsen gastro-oesophageal reflux symptom perception in women(Watson et al., 1997b, Welen et al., 2008). Most of these theories need further evidence based on prospective randomised studies.

1.2.1 Risk Factors

1.2.1.1 *Obesity*

A systematic review and meta-analysis by Nirwan et al. found that the prevalence of gastro-oesophageal reflux disease rises with an increase in body mass index (BMI)(Nirwan et al., 2020). Complications secondary to reflux disease, including the risk of Barrett's oesophagus and oesophageal malignancy, have a strong correlation with central adiposity, and this effect is independent of body mass index(Singh et al., 2013). Central obesity can lead to a mechanical disruption of the normal anatomy of gastro-oesophageal junction and increased pressure gradient across lower oesophageal sphincter due to increased intra-abdominal and intragastric pressure, which may precipitate the development of a hiatus hernia. At a cellular level, gastro-oesophageal reflux disease patients with central adiposity have increased permeability of the distal oesophageal epithelium, indicative of a compromised epithelial barrier(Blevins et al., 2018). It therefore makes sense that reflux disease symptoms may improve with a reduction in body mass index and, specifically, a decrease in waist circumference(Richter and Rubenstein, 2018). Other contributing factors include:

1.2.1.2 *Smoking*

The systematic review by Nirwan et al., 2020 also found that active smokers had a higher prevalence of gastro-oesophageal reflux disease compared to ex-smokers and non-smokers(Nirwan et al., 2020). The lower oesophageal sphincter resting pressure is reduced by nicotine leading to gastric content reflux into oesophagus(Sloan et al., 1992). Smoking also extends the oesophageal acid clearance time due to depletion of salivary secretion and bicarbonate concentration(Dent et al., 1980).

1.2.1.3 *Dietary factors and acidic beverages*

Fatty food delays gastric emptying; reduces lower oesophageal sphincter pressure and leads to an increase of transient lower oesophageal sphincter relaxations. Acidic juices, including orange, grapefruit, and tomato juice, may promote reflux disease by exacerbating the effect of gastric reflux on

the distal oesophageal mucosa. Moderate to heavy carbonated beverages may also cause reflux by reducing lower oesophageal sphincter pressure(El-Serag et al., 2005, Shapiro et al., 2007).

1.2.1.4 *Concomitant diseases*

One third of diabetics have an increased likelihood of reduced oesophageal contraction amplitude, reduced lower oesophageal sphincter resting pressure, and delayed bolus transit time leading to an increased incidence of reflux disease(Kong et al., 1999). Gastro-oesophageal reflux disease is also prevalent in asthmatics, ranging between 30% and 90% of cases(Havemann et al., 2007). Patients with connective tissue disorders (including scleroderma, systemic lupus erythematosus, dermatomyositis, and others) can develop gastro-oesophageal reflux disease and complications due to oesophageal dysfunction and concomitant reduced lower oesophageal sphincter pressure(Patti et al., 2008).

1.2.1.5 *Other risk factors*

Other risk factors for gastro-oesophageal reflux disease may include a lower educational level, poor socio-economic status, or low-income group, being divorced, widowed or separated. Nonsteroidal anti-inflammatory drug, aspirin, and glucagon-like peptide-1 agonists are independent risk factors for gastro-oesophageal reflux disease, likely by increasing the duration of acid reflux (El-Serag et al., 2004, Nocon et al., 2006, Nirwan et al., 2020, Kotzan et al., 2001, Ruigomez et al., 2004, Ruszniewski et al., 2008). However, exact mechanisms mediating the likely association of lower educational level and socio-economic status linked as a risk factor for gastro-oesophageal reflux disease is not known and further studies are needed for clarification.

1.2.2 Clinical manifestations of gastro-oesophageal reflux disease

1.2.2.1 *Typical symptoms*

Heartburn, a retrosternal burning sensation typically after meals, and volume regurgitation, with gastric content reflux into the upper oesophagus, throat, or mouth, are considered cardinal symptoms of gastro-oesophageal reflux disease and referred to as typical or oesophageal symptoms (Vakil et al., 2006).

1.2.2.2 *Atypical symptoms*

Asthma, chronic cough, hoarseness, and laryngitis are less common symptoms of gastro-oesophageal reflux disease and referred to as atypical or extra-oesophageal symptoms. Atypical symptoms may be caused by gastric content reflux causing irritation and bronchoconstriction. However, atypical symptoms are not always due to reflux disease and may have an entirely separate pathophysiology.

Table 1-1 Gastro-oesophageal reflux symptoms

TYPICAL SYMPTOMS	ATYPICAL SYMPTOMS
– Heartburn – Regurgitation	– Chronic cough – Hoarseness of voice or Laryngitis – Non-cardiac chest pain – Asthma, Throat clearing, Globus

1.2.2.2.1 Asthma

Gastro-oesophageal reflux disease is commonly reported in asthmatic patients. The prevalence of reflux symptoms in asthma is almost 60% in a systematic review consisting of 28 studies, compared to 38% in controls (Havemann et al., 2007, Harding, 2005). The most likely mechanism is bronchoconstriction due to micro-aspiration of gastric reflux into the proximal airways. This may increase bronchial reactivity and may also increase vagal tone which may exacerbate asthma-related symptoms (Harding, 2005, Havemann et al., 2007, Herve et al., 1986, Karbasi et al., 2013, Ricciardolo et al., 1999).

1.2.2.2.2 Chronic cough

About 40% of patients with gastro-oesophageal reflux disease show no apparent symptoms other than a chronic cough (Kastelik et al., 2005, Irwin et al., 1993, Smyrnios et al., 1995). Reflux disease may

induce a cough via several mechanisms, which include aspiration of gastric contents, stimulation of receptors in the upper respiratory tract, or trigger of the oesophageal-tracheobronchial cough reflex by the presence of acid in the distal oesophagus (Fontana and Pistolesi, 2003, Kahrilas et al., 2016).

1.2.2.2.3 Laryngitis

Laryngitis, caused by the laryngopharyngeal reflux, may include the following symptoms: hoarseness, mild dysphagia, globus sensation, and non-productive throating clearing. These are collectively less common extra-oesophageal manifestations of gastro-oesophageal reflux disease. Reflux disease may cause laryngitis directly by the reflux of gastric contents into the larynx or indirectly by the activation of vagal tone through acid reflux in the oesophagus (Ford, 2005).

Alarm symptoms suggesting complications of gastro-oesophageal reflux disease include dysphagia, odynophagia, weight loss, haematemesis and malaena (Vakil et al., 2006).

Table 1-2 Gastro-oesophageal reflux disease alarm symptoms and complications

ALARM SYMPTOMS	COMPLICATIONS
– Dysphagia	– Oesophagitis
– Odynophagia	– Oesophageal ulcers
– Weight loss	– Peptic stricture
– Malaena	– Barrett's oesophagus
– Hematemesis	– Oesophageal adenocarcinoma

1.2.3 Diagnosis of gastro-oesophageal reflux disease

The diagnosis of gastro-oesophageal reflux disease relies on a good history to ascertain the presence of typical versus atypical symptoms as well as response to anti-reflux medication, in addition to objective testing. Objective testing usually entails an upper endoscopy and/or ambulatory pH monitoring. The modern diagnosis of reflux disease (described in the Lyon consensus v2.0) recommends defining individual reflux disease patient phenotypes based on refluxate exposure, reflux mechanism, clearance efficacy, gastro-oesophageal junction anatomy and psychometrics defining symptomatic presentations (Gyawali et al., 2023).

1.2.4 Clinical history

Empirical PPI therapy (PPI trial) is a routine initial approach to assess the possibility of gastro-oesophageal reflux disease when it is suspected in patients with typical symptoms. Whereas patient with chest pain and suspected gastro-oesophageal reflux disease should have diagnostic evaluation before initiation of therapy to rule out cardiac or alternative causes. However, there is a changing sentiment due to the explosive cost for PPIs to countries pharmaceutical schemes. The initial step with testing for objective evidence is looking more cost effective as recommended in the Lyon consensus 2.0 (Gyawali et al., 2023). In a study conducted by Morgenthal et al., patients with atypical symptoms were significantly more likely to have an unsuccessful outcome (OR 7.8) after empirical proton pump inhibitor therapy. Only 41% of these patients had a successful outcome, compared to a success rate of 85% in patients with typical symptoms (Morgenthal et al., 2007c). Typical symptoms predicted successful outcomes in studies evaluating anti-reflux procedures as well, with an odds ratio of 4.3–5.1 (Campos et al., 1999, Jackson et al., 2001).

1.2.5 Endoscopy and biopsies

Although endoscopy is not required or recommended for the initial evaluation of patients with typical reflux symptoms, it is recommended in patients who do not respond to initial PPI treatment, or when they present with alarm symptoms including: new onset dysphagia in patients older than 60 years of age, evidence of gastro-intestinal bleeding (including iron deficiency anaemia), anorexia, unexplained weight loss, odynophagia or persistent vomiting (DeVault et al., 2005). Using the Los Angeles

classification (Lundell et al., 1999) based on the extent of erosions or mucosal breaks in the distal oesophagus, findings of LA grades B, C and D oesophagitis, biopsy proven Barrett's mucosa and peptic oesophageal stricture are conclusive evidence for gastro-oesophageal reflux disease as per the Lyon consensus 2.0 (Gyawali et al., 2023). Endoscopy is usually the first diagnostic modality in the evaluation of patients who have persistent reflux symptoms despite optimal medical management for gastro-oesophageal reflux disease, which is twice daily PPI 40mg for 8 weeks (Naik et al., 2020). PPI should be stopped before performing endoscopy. Based on the endoscopic findings, 25% of patients with reflux symptoms had evidence of erosive oesophagitis or erosive reflux disease and 75% had non erosive reflux disease or NERD (Ronkainen et al., 2005).

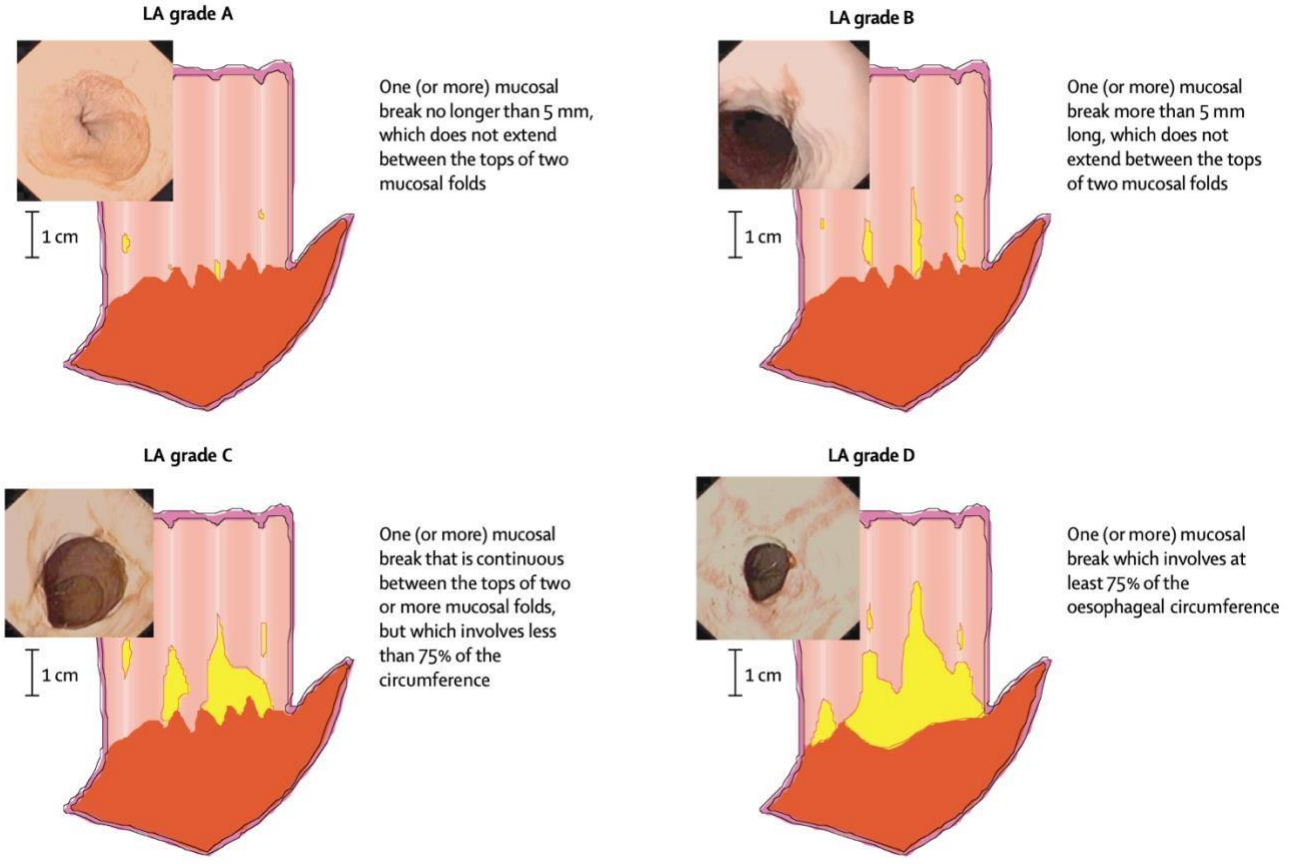


Figure 1-5: Los Angeles classification of oesophagitis Adapted from Gastro oesophageal reflux disease Reproduced with permission from Paul Moayyedi, Nicholas J Talley , (Moayyedi and Talley, 2006)

Repeat endoscopy should be performed in patients with severe erosive reflux disease after treatment with anti-secretory therapy to exclude underlying Barrett's oesophagus(Wang et al., 2008a).

1.2.6 Reflux monitoring

Ambulatory oesophageal pH monitoring is the gold standard investigation for patients with gastro-oesophageal reflux disease being considered for anti-reflux surgery. Ambulatory reflux monitoring allows the direct measurement of oesophageal acid exposure (acid exposure time; AET), reflux episode frequency, and association between symptoms and reflux episodes to provide confirmatory evidence of reflux disease. It is most useful in patients who have: a normal endoscopy; those with atypical symptoms; and in those being considered for anti-reflux surgery (Roman et al., 2017). 24 h pH-metry monitoring records the presence of acid in the distal oesophagus during 24 hours of monitoring by means of a transnasal pH catheter positioned 5cm above the proximal margin of the lower oesophageal sphincter (located on manometry) or wireless pH monitoring with capsule placed 6cm above the Z-line /gastro-oesophageal junction (Morgenthal et al., de Caestecker and Heading, 1990, Singh et al., 1992). When there is reflux of acidic gastric contents into the lower oesophagus, there is a decrease in the oesophageal pH. A reflux episode is defined as a decrease in oesophageal pH below pH 4 for a period longer than 5 seconds (Johnsson and Joelsson, 1988, Schindlbeck et al., 1991, Wallin and Madsen, 1979, Wiener et al., 1988a). After 24 hours, the transnasal catheter is removed, and the pH data for the 24-hour monitoring is analysed. Results are expressed using six standard components. From these 6 parameters, a DeMeester Score is determined by calculating the number of standard deviation equivalents in each measured value, which is a global measure of distal oesophageal acid exposure (Johnson and DeMeester, 1986). A DeMeester score (DMS) > 14.72 indicates the presence of pathological reflux (Ayazi et al., 2009b). The score is interpreted as no GORD if DMS <14.72, mild GORD between 14.72 and 50, moderate for 51 – 100, and severe GORD if DMS >100. pH monitoring with composite scoring is a reliable method for clinical decision making (Johnson and Demeester, 1974, DeMeester et al., 1999, Neto et al., 2019).

Monitoring components	**Normal values**
Percent time pH < 4	<4.2% (1.47 ± 1.38)
No. of reflux episodes	<50 (18.93 ± 13.78)
No. of reflux episodes > 5 min	3 or less (0.64 ± 1.28)
Longest reflux episode (minutes)	<9.2 min (3.83 ± 2.78)
Supine period	<1.2% (0.286 ± 0.467)
Upright period	<6.3% (2.33 ± 1.97)
Composite score	<14.7
Data displayed as 95th percentile	

Figure 1-6: DeMeester score – from 24-hour pH monitoring of acid reflux

While monitoring reflux, a fall in oesophageal pH < 4 for more than 6% of 24 hour monitoring is interpreted as abnormal distal oesophageal acid expsoure time. Abnormal acid exposure time distinguishes symptomatic patients from controls(Johnsson and Joelsson, 1988, Schindlbeck et al., 1991). Reflux monitoring can confirm or exclude pathological gastro-oesophageal reflux disease, although not always conclusively.

The primary outcome of a 24-hour pH-metry study is acid exposure time. An extended recording time of 48 or 96 hours with a wireless pH monitoring system increases the diagnostic yield compared to 24 hour recording (Sweis et al., 2011, Ayazi et al., 2009a) and test reproducibility. This is particularly useful when a trans-nasal catheter is not tolerated or yielded a negative result despite a high suspicion of gastro-oesophageal reflux disease (Sweis et al., 2011). However, wireless pH monitoring is expensive, limiting its availability. There are limitations with the use of 24 h-pH-metry for the diagnosis of gastro-oesophageal reflux disease. The frequency of symptoms is variable and may not occur during a routine 24-hour monitoring session. Also, standard pH monitoring cannot diagnose non-acidic reflux events (pH> 4) (Vaezi and Shay, 2001). Another variation on reflux monitoring is multichannel intraluminal pH impedance monitoring, which characterises reflux events with both a pH electrode and a series of

impedance electrodes. pH-impedance measurement permits the detection of anterograde and retrograde bolus (liquid, gas or mixed) flow in the oesophagus and combined impedance-pH monitoring allows for the chemical characterization of the refluxate. pH-impedance monitoring can detect not only acidic (pH < 4) but also weakly acidic (pH 4 - 7) and non-acidic (pH > 7) reflux of gastric contents. This increases the diagnostic yield of 24-h reflux monitoring in patients with reflux symptoms.

Since pH-impedance detects all reflux (liquid, gas or mixed) regardless of acidity, and defines the direction of flow, it is considered the gold standard (Roman et al., 2017, Sifrim et al., 2004). However, as the added yield is limited in patients with classical acidic reflux (Savarino et al., 2012, Frazzoni et al., 2013a), the test is not widely utlilised; there are additional hardware costs, and the data analysis and interpretation are laborious.

Acid exposure time is calculated as the percentage of time the pH is less than pH 4 in the distal oesophagus. The Lyon consensus proposes that acid exposure time < 4% be considered normal (physiological) and > 6% be considered abnormal. Intermediate values identify a “grey area” or equivocal findings, in which additional evidence from other tests are required for evidence of pathologic acid burden (Gyawali et al., 2023).

Symptom reporting during ambulatory 24-hour pH monitoring enables analysis of the temporal relationship between reflux and symptoms. The pH-impedance test enables further enhanced analysis of acid and non-acid reflux and proximal extent of reflux, useful to assess atypical gastro-oesophageal reflux disease manifestations such as cough, asthma, laryngitis, and non-cardiac chest pain (Bigatao et al., 2018, Pauwels et al., 2009).

Ambulatory oesophageal reflux monitoring has additional benefit of correlating symptoms with reflux episodes (Johnsson et al., 1987). Scoring systems were developed to attribute symptoms of heartburn, regurgitation and chest pain to reflux episodes. One such score is Symptom Index or SI defined as percentage of symptom episodes related to reflux events defined by the number of symptoms associated with pH < 4 divided by the total number of symptoms during the same period expressed as a percentage (Wiener et al., 1988b). A SI > 50% is considered positive. Another scoring system is Symptom Association Probability or SAP, a statistical probability or likelihood of symptom-reflux-

association; positive SAP is defined as >95% probability that symptom events are associated with reflux events (Hirano et al., 2007).

1.2.7 High Resolution Manometry

High resolution manometry measures oesophageal luminal pressures and co-ordination of the pressure activities of lower oesophageal sphincter, body, and upper oesophageal sphincter. It can detect physiological abnormalities associated with reflux disease such as a low distal oesophageal contractility index, hypotensive lower oesophageal sphincter/ gastro-oesophageal junction (GOJ) pressure, hiatus hernia, or ineffective oesophageal peristalsis. While manometry is useful to detect unsuspected adynamic oesophagus and/or achalasia, a functional obstruction due to failure of relaxation of the lower oesophageal sphincter (Faria et al., 2013, Pandolfino et al., 2005), it may not be mandatory in some parts of the world where there is increasing use of an alternative, a functional lumen imaging probe or FLIP REF missing. Achalasia, with failure of lower oesophageal sphincter relaxation, usually presents with dysphagia, along with other symptoms of heartburn and/or regurgitation, simulating reflux disease, but achalasia is a contraindication for fundoplication (Kessing et al., 2011, Spechler et al., 1995).

1.3 Management of gastro-oesophageal reflux disease

The aim of treatment for patients with gastro-oesophageal reflux disease is to provide resolution or improvement of symptoms. Initially this is achieved with lifestyle modifications in combination with anti-secretory medication. In normal practice, reflux disease patients with typical symptoms can be started on empiric treatment with anti-reflux medication(Katz et al., 2013). However, the decision to investigate with objective investigations depends on the physician's assessment of symptoms and risks. The presence of atypical symptoms, poor response to anti-reflux medication despite maximal dose, and the presence of alarm symptoms (as mentioned earlier), would warrant urgent endoscopic evaluation.

1.3.1 Lifestyle modifications

This involves the following strategies:

- Avoid certain food and beverages, including alcohol, caffeine, carbonated drinks, and citrus juices, that induce reflux or heartburn.
- Weight loss, with the aim of achieving a normal body mass index.
- Smoking cessation to help control reflux symptoms and reduce the incidence of oesophageal adenocarcinoma.
- Eating the evening meal before 7 pm, or 3 to 4 hours before going to bed.
- Elevate the head of the bed to 30 degrees and/or use a foam wedge under the mattress/blocks under the head of the bed to prevent reflux when supine.

The literature supporting the above measures are weak(Kaltenbach et al., 2006, Kahrilas et al., 2008), but there is no harm to instituting them in the first instance.

1.3.2 Pharmacologic treatment

In clinical practice, the diagnosis of gastro-oesophageal reflux disease is often a clinical diagnosis, and treatment pathway is based on patient's symptom presentation and assessment. Reflux disease patients are subjected to diagnostic testing if they fail to respond to anti-secretory medications or if there is uncertainty about diagnosis and/or whilst treating,preventing gastro-oesophageal reflux disease complications.

The purpose of using acid suppressant medication is to inhibit or reduce gastric acid production to reduce acid reflux into the lower oesophagus.

1.3.2.1 *Proton pump inhibitors*

Proton pump inhibitors are indicated when lifestyle modifications and use of over-the-counter antacid formulations to neutralise acid reflux (various compounds with various salts of calcium, magnesium, and aluminum as active ingredients) fail to control symptoms of gastro-oesophageal reflux disease. Proton pump inhibitors are the most dominant class of drugs which inhibit gastric acid secretion in the stomach and are considered the mainstay of medical treatment for gastro-oesophageal reflux disease, particularly in patients with non-erosive reflux disease (Sigterman et al., 2013). They are highly effective in treating all grades of oesophagitis, controlling symptoms, and preventing complications, though patients need to remain on maintenance therapy, to sustain remission. Patients with gastro-oesophageal reflux disease who fail once daily therapy are trialed with double-dose therapy to improve healing of oesophagitis (Richter and Bochenek, 2000). However, proton pump inhibitors are not endorsed for controlling atypical symptoms of reflux disease and complications (Moore and Vaezi, 2010). Proton pump inhibitors are safe, and side effects like headache and diarrhoea occur in less than 5% of patients, which are reversible upon cessation of PPIs. However longer-term proton pump inhibitor treatment is associated with vitamin B12 and magnesium deficiency, increased risk of gastroenteritis, *Clostridium difficile* colitis, ischaemic heart disease, chronic renal impairment, and dementia (Lazarus et al., 2016, Gomm et al., 2016). Hence, patients with gastro-oesophageal reflux disease on long term inhibitor therapy should remain on the lowest possible dose to control symptoms and their need for long-term proton pump inhibitors should be reassessed at 12 months. Patients who suffer adverse events from inhibitor therapy should be considered for surgery.

1.3.2.2 *Histamine-2 receptor antagonists or (H2RAs)*

Histamine-2 receptor antagonists are a less potent class of anti-secretory medication compared to proton pump inhibitors (Sigterman et al., 2013). Hence, these are used mostly as step-down treatment following proton pump inhibitor induced remission in patients with uncomplicated gastro-oesophageal reflux disease, and in patients who are intolerant to proton pump inhibitors. At times, they are also

instituted alongside inhibitor therapy to enhance gastric acid suppression by prolonging the duration of intragastric pH more than pH 4 (Abdul-Hussein et al., 2015).

Other commonly used medications include Carafate, Antacids, and Vonoprazan.

1.3.3 Surgical treatment

Gastro-oesophageal reflux disease is a common ailment, faced by medical professionals for over a century and the incidence has risen in recent times, especially in developed nations (Nirwan et al., 2020). Reflux disease has a heterogeneous manifestation, and its diagnosis can be challenging. Although first-line treatment is with lifestyle modifications and anti-reflux medication, roughly one third of reflux disease patients do not respond (El-Serag et al., 2010). For these individuals, a laparoscopic fundoplication is a welcome alternative. The surgery was introduced in 1991 by the laparoscopic approach and it has since replaced the conventional technique (Nissen, 1956, Dallemagne et al., 1991). Studies have shown shorter hospital stay, faster recovery with less pain, and excellent long-term subjective and objective outcomes with better quality of life and relief of symptoms after laparoscopic fundoplication (Dallemagne et al., 2006, Morgenthal et al., 2007c).

Compared to medical therapy, laparoscopic fundoplication is more effective in the short- and medium-term follow-up regarding subjective outcomes for reflux disease patients' post-surgery(Rickenbacher et al., 2014). An extensive Cochrane review, however, while comparing medical *vs* the surgical modes of treatment, suggested further randomised controlled trials with an outcome assessor blinding, to achieve a more conclusive recommendation(Garg and Gurusamy, 2015). Currently, the most common indications for surgical treatment by laparoscopic fundoplication are:

- Adverse effects from anti- reflux medication therapy
- Young patients who do not want long-term medical therapy
- Gastro-oesophageal reflux disease with a large hiatus hernia
- Volume regurgitation
- Pathological distal oesophageal acid exposure or ongoing oesophagitis on maximal proton pump inhibitor therapy

- Breakthrough symptoms on maximal proton pump inhibitor therapy

Studies have found that laparoscopic fundoplication is a cost-effective option for the treatment of patients with gastro-oesophageal reflux disease, with improved quality of life in short-, and long-term follow-up, compared to maintenance PPI therapy (Goeree et al., 2011, Cookson et al., 2005). However, the success rate after laparoscopic fundoplication is 85-90% and this has not changed in the past 20 years (Salminen, 2009, Hoshino et al., 2017, Omura et al., 2018).

1.4 Predictors of success

Laparoscopic fundoplication has been the gold standard surgical option for advanced gastro-oesophageal reflux disease since the mid-1990s with close to 85-90% patient satisfaction rate at 10 years. Most patients experience symptom relief or improvements in symptoms, a better quality of life, and resolution of oesophagitis and reduced or eliminated gastro-oesophageal reflux on objective testing (Omura et al., 2018, Morgenthal et al., 2007c).

However, a universally accepted definition of a successful outcome after anti-reflux surgery for gastro-oesophageal reflux disease has not been established. Most studies base their clinical outcomes on subjective results such as patient satisfaction, quality of life and percentage of patients requiring anti-reflux medications after surgery or requiring revision fundoplication after the primary fundoplication. Lundell et al. defined failed anti-reflux surgery when at least one of the following criteria was present: persistence or recurrence of moderate to severe heartburn or regurgitation occurring more than once every two weeks (grade 2) or daily (grade 3) or both; moderate to severe dysphagia reported in combination with heartburn or regurgitation or both; the use of daily or weekly PPI medication; endoscopic evidence of erosive esophagitis Savary Miller grade 1-4; pathological acid reflux on 24-h pH monitoring; and necessity to undergo redo/revisional surgery (Lundell et al., 2001).

1.4.1 Pre-operative patient factors

1.4.1.1 *Age, Gender, and Socio-Economic Status*

A study by Beck et al. in 2009 investigated the impact of sex and age on longer-term clinical outcomes following laparoscopic fundoplication and found that age did not influence the outcome of laparoscopic fundoplication. However, post-operative outcomes were worse in females compared to males, and revisional procedures occurred more frequently in females (Beck et al., 2009). In a large prospective non-randomized observational cohort study, Fei et al. evaluated the influence of age on the outcome of laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. They concluded that laparoscopic anti-reflux surgery was a safe and effective treatment for reflux disease in elderly patients, with low morbidity and mortality rates (Fei et al., 2013a). On the other hand, O'Boyle et al found that male sex and private health insurance were the strongest predictors of satisfaction with the overall outcome after fundoplication (O'Boyle et al., 2002). Most studies included in the review

defined elderly as more than or 70 years of age, however some studies referred to elderly as more than 65 years of age.

1.4.1.2 *Body Mass Index (BMI)*

Multiple studies have analysed the predictive role of obesity in patients with reflux disease by using body mass index, defined as a person's weight in kilograms divided by the square of height in metres, by categorising them in healthy range of 18.5 to <25 kg/m^2, overweight 25 to <30 kg/m^2, Obesity class 1/low risk 30 to <35 kg/m^2, Obesity class 2/moderate risk if >35 kg/m^2 to 39.9 kg/m^2 , and Obesity class 3/high risk if > 40 kg/m^2 .Typically, a body mass index of >35 kg/m^2 has been used as a cut-off for patient selection for a laparoscopic fundoplication (Mechanick et al., 2013). Chisholm et al., in 2009, looked at this issue with a sample size number of 481 patients. After dividing them into the above three weight categories, they found no significant differences between groups aside from significantly longer operating times (Chisholm et al., 2009). D'Alessio et al. prospectively assessed 257 patients who underwent laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease and found similar complication rates for all body mass index categories. In addition, the number of patients who achieved good or excellent clinical outcomes was similar across all BMI groups. However, this study had a mean follow-up of 25.5 months, and only three patients were in high-risk obesity class (D'Alessio et al., 2005a). Winslow et al. in his study evaluated a large patient cohort of 505 patients of which 76 were high-risk obese (BMI ≥ 35 kg/m2). Mean follow-up was 35 months. They found that symptom relief and complication rates were similar across all body mass index categories (Winslow et al., 2003b).

1.4.1.3 *Typical Vs. Atypical Symptoms*

Morgenthal et al. found that patients with atypical symptoms were significantly more likely to have an unsuccessful outcome (Odd ratio, OR 7.8) with only 41% of these patients reporting a successful outcome, compared to 85% of patients with typical symptoms (Morgenthal et al., 2007a). Despite these findings, well-selected patients with atypical symptoms may benefit from laparoscopic fundoplication. Allen and Anvari found that patients whose cough responded to proton pump inhibitor treatment and replication of symptom with mid-oesophageal acid infusion (Bernstein test), then had a greater improvement in cough post-operatively than those not meeting these criteria (Allen and Anvari, 2002).

1.4.1.4 *Response to proton pump inhibitors or anti-reflux medication*

Some patients experience only partial relief from reflux symptoms after optimized medical treatment with proton pump inhibitors, and they are referred to as partial responders. Patients with no response to medical therapy were more likely to have a failed outcome after fundoplication (OR 2.6) compared to those with at least a partial symptom response. The University of Southern California group found a partial or complete response to proton pump inhibitor therapy conferred an odds ratio of 3.3, while Jackson et al. found an odds ratio of 6.5 when comparing complete responders to partial or non-responders (Campos et al., 1999, Jackson et al., 2001). A systematic review on partial responders by Lundell et al. concluded that although there was a substantial reduction in the prevalence of heartburn and regurgitation immediately after anti-reflux surgery, symptoms recurred in 30%-35% of patients after a ten-year follow-up (Lundell et al., 2014).

1.4.1.5 *Refractory gastro-oesophageal reflux disease*

The presence of persistent, troublesome reflux symptoms with objective evidence of gastro-oesophageal reflux disease despite optimised or optimal proton pump inhibitor therapy is defined as proton pump inhibitor refractory gastro-oesophageal reflux disease (Zerbib et al., 2021). Of all patients with reflux disease on proton pump inhibitor therapy, 40% may experience inadequate relief with proton pump inhibitors. Some of these do not have gastro-oesophageal reflux disease to begin with, and the rest may have proton pump inhibitor refractory reflux disease. Partial proton pump inhibitor response, according to the Lyon Consensus 2.0, is the presence of mild heartburn and/or regurgitation on 3 or more days per week despite at least 4 weeks of proton pump inhibitor therapy (Gyawali et al., 2023). If symptoms persist despite adequate therapy, it is important to establish that the patient's symptoms are indeed due to reflux disease. Therefore, the next appropriate step is oesophageal pH monitoring with or without impedance testing (off PPI therapy). Other conditions mimicking proton pump inhibitor-refractory gastro-oesophageal reflux disease is common, such as rumination syndrome, functional heartburn, and acid reflux hypersensitivity should be ruled out to avoid misdiagnosis and mismanagement. Schwameis et al. in their study concluded that patient satisfaction after Nissen fundoplication was excellent and independent of response to proton pump inhibitor therapy. Therefore, anti-reflux surgery remains an option for patients with heartburn and confirmed gastro-

oesophageal reflux disease regardless of the degree of symptom response to PPI (Schwameis et al., 2020).

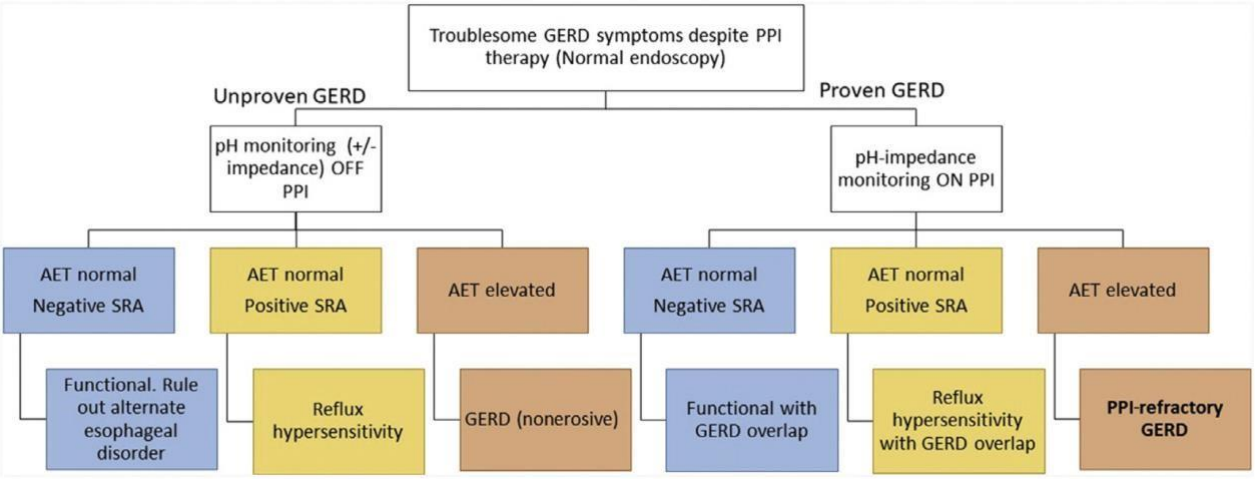


Figure 1-7: Role of pH testing to identify causes of PPI nonresponse. AET (Acid Exposure Time); SRA, (Symptom-Reflux Association. Used with permission from Rena Yadlapati, MD, MSHS, Kelli DeLay, MD Proton Pump Inhibitor– Refractory Gastroesophageal Reflux Disease Med Clin N A (Yadlapati and DeLay, 2019)*

1.4.1.6 *Psychosocial Factors*

Depression is independently associated with worse post-operative quality of life after fundoplication (Statz et al., 2017). Given that depression is a co-morbid condition in 30%–65% of patients with gastro oesophageal reflux disease, this is an important comorbidity to consider pre-operatively (Bilgi et al., 2017). Several studies have examined the impact of depression on laparoscopic surgery outcomes. Power et al. studied 131 patients who underwent laparoscopic Nissen fundoplication and found that pre-operative depression and psychogenic stressors were associated with failure after laparoscopic Nissen fundoplication (Power et al., 2004). Similarly, Kamolz et al. found that patients with reflux disease and depression had significantly higher rates of post-operative chest pain (44.7% vs. 2.6%), bloating (68.4% vs. 18.4%), and dysphagia (50.1% vs. 2.6%) after fundoplication when compared to reflux disease patients without depression (Kamolz et al., 2003b).

1.4.1.7 *High Volume Vs. Low Volume Centre*

A few low-volume centres have published their results after laparoscopic fundoplication and have shown it is a safe procedure with post-operative results comparable to high volume centres (Prassas et al., 2017). However, Schlottmann et al., in a large cohort study, found that when anti-reflux surgery is performed in high-volume hospitals, morbidity is lower, length of hospital stay is shorter, and costs for the healthcare system are decreased (Schlottmann et al., 2018).

1.4.1.8 *Pre-Operative Grading of Oesophagitis*

According to the Lyon consensus 2.0, endoscopic evidence of oesophagitis, biopsy proven Barrett's mucosa, and oesophageal peptic stricture are objective evidence of GORD (Gyawali et al., 2023). Laparoscopic Nissen fundoplication is a suitable therapeutic strategy for all patients with objectively proven GORD selected for surgery, irrespective of their pre-operative oesophagitis grade (Watson et al., 1997a).

1.4.1.9 *Gastric stasis or Gastroparesis*

Many patients referred for anti-reflux surgery have associated symptoms suggestive of delayed gastric emptying such as bloating, nausea, vomiting, and abdominal pain and/or fullness. It is not uncommon for these patients to have objective evidence of gastroparesis on a gastric emptying study REF missing. Some patients have a generalized gastrointestinal tract motility disorder and others a true isolated gastroparesis. Controversy exists in the literature regarding whether these patients will have poor outcome if offered anti-reflux surgery. This is also compounded by the fact that post-operative retching or vomiting will lead to wrap herniation or disruption.

Many physicians consider it important to establish whether delayed gastric emptying is present pre-operatively (Masqusi and Velanovich, 2007). On the other hand, some physicians challenge the usefulness of pre-operative screening for delayed gastric emptying, even in patients with pre-operative symptoms suggestive of gastroparesis, arguing that this will improve after fundoplication (Bais et al., 2001b).

Currently, there are no clear guidelines on how to treat patients with reflux disease and associated delayed gastric emptying. Some investigators strongly advocate pyloroplasty for all patients with evidence of delayed gastric emptying, whereas others suggest that pyloroplasty should only be

considered in patients who have moderate to severe objective gastroparesis (Farrell et al., 2001). Some argue against any intervention. Farrell et al. reported an 86.3% symptomatic success rate in patients with gastroparesis (n = 15) compared to 91.8% without gastroparesis (Farrell et al., 2001). Similar results were demonstrated by Bais and colleagues in a prospective study of 36 patients (Bais et al., 2001a). Khajanchee et al. in a retrospective analysis demonstrated that delayed gastric emptying did not affect post-operative outcomes following Nissen fundoplication, but found increased gas bloat and/or nausea in those with gastroparesis. They found this could be corrected with the addition of a pyloroplasty (Khajanchee et al., 2009). On the other hand, when evaluated with radionuclide gastric emptying studies, mild to moderate delayed gastric emptying was associated with weakly acidic reflux and it was an independent risk factor for a poor outcome after laparoscopic fundoplication (Rebecchi et al., 2013).

Tog et al., in a recent study, quantified the incidence of delayed gastric emptying (defined as endoscopic evidence of solid food in the stomach after fasting for 6h) at 6 months following laparoscopic fundoplication for large hiatus hernia (> 50% of stomach in chest). They found that delayed gastric emptying occurred in 19 of 102 patients (18·6 per cent) and was associated with adverse symptoms and reduced patient satisfaction (Tog et al., 2017). The postulation was that the combination of extensive sac dissection, oesophageal mobilization, and gastric fundus manipulation predisposed to accidental vagotomy (Vu et al., 2000, Lindeboom et al., 2004).

1.4.2 Operative Factors

1.4.2.1 *Operative time*

Laparoscopic fundoplication is a safe and feasible procedure as proven in several studies, though it requires minimally invasive surgery expertise. While the surgery can be performed in the most common 2D video, laparoscopic fundoplication through 3D vision has been found to have minor additional advantage of enhanced visualisation and better spatial perception (Leon et al., 2017). This is important as longer operative times have been associated with higher rates of complications (Jackson et al., 2011). Melvin et al, in 2002, compared robotic assisted versus laparoscopic conventional fundoplication to find significantly longer operative times in the first group, but comparable post-operative complication rates and lengths of stay between the two groups (Melvin et al., 2002). Cadière et al. published similar

results, showing an increased operative time in the robotic-assisted fundoplication group, but no significant differences in morbidity and mortality compared with laparoscopic surgery (Cadiere et al., 2001). Villamere et al. demonstrated no statistically significant differences in major complications and in-hospital mortality between 2D laparoscopic and robotic-assisted anti-reflux surgery groups. The anti-reflux robotic assisted group had longer length of stay and a higher 30-day re-admission rate (Villamere et al., 2015).

1.4.2.2 *Surgeon Experience and Learning Curve*

Studies show that learning curve-related difficulties such as prolonged operating time, higher conversion rates, increased number of complications, and higher re-operative rates are more likely during the first twenty cases performed by each individual surgeon, with learning curve-related difficulties eliminated after this level of expertise (Voitk et al., 1999, Watson et al., 1996). This was confirmed in a study by Salminen et al. that showed no improvement on post-operative outcomes beyond the learning curve (Salminen et al., 2007a).

1.4.2.3 *Type of Fundoplication*

Laparoscopic Nissen 360^{o} fundoplication is a commonly performed anti-reflux procedure (Broeders et al., 2009c, Salminen et al., 2007b, Draaisma et al., 2006). Partial fundoplication was developed as an alternative for the Nissen fundoplication, with the aim of reducing the high incidence of post Nissen troublesome dysphagia and gas-related symptoms, such as gas bloating, flatulence, and inability to belch (Broeders et al., 2013b). Several randomised controlled trials and meta-analyses evaluated whether a partial fundoplication reduces post-fundoplication symptoms (i.e., bloating, dysphagia, and increased flatulence) at the expense of inferior reflux control compared with laparoscopic Nissen fundoplication. Both laparoscopic Toupet 270^{o} posterior and laparoscopic 180° anterior fundoplication provide similar reflux control, with a lower rate of post-operative dysphagia and gas-related symptoms compared with laparoscopic Nissen fundoplication (Varin et al., 2009, Broeders et al., 2013b). In fact, results from a recent randomised controlled trial by Hakanson et al. did not find any differences in reflux control nor improvement in quality of life between total and partial fundoplication, when assessed over a 5-year period (Hakanson et al., 2019). However, some studies show a statistically significant difference in dysphagia in favour of a partial fundoplication after 1 and 2 years (Broeders et

al., 2010b, Catarci et al., 2004, Baigrie et al., 2005, Broeders et al., 2013a, Khan et al., 2010, Koch et al., 2012, Ludemann et al., 2005, Strate et al., 2008). The most performed partial fundoplication is either the posterior 270° fundoplication (Toupet) or the anterior 180° fundoplication (Broeders et al., 2013b, Stefanidis et al., 2010). Two randomised trials, one by Engstrom et al., 2007 and the second by Daud et al., 2015, compared a 270° posterior partial fundoplication to a 180° anterior partial fundoplication. They found similar levels of satisfaction between the two partial wraps, but highlighted trade-offs between reflux control and side-effects. Inability to belch was more common after a posterior partial fundoplication, but heartburn scores were higher after an anterior 180° partial fundoplication at 12 months, consistent with a trend towards higher acid exposure time. Dysphagia rates were similar between the two groups at all time points (Engstrom et al., 2007, Daud et al., 2015). Moreover, a 2017 trial by Roks et al. randomised twice as many patients and the results were similar to the study by Daud et al. A possible advantage of a laparoscopic 180° anterior partial fundoplication compared to a 270° posterior partial fundoplication may be that the former requires no division of the short gastric vessels, although operative times did not differ significantly between the two techniques (Roks et al., 2017). A meta-analysis by Memon et al. in 2015 comparing laparoscopic anterior fundoplication to posterior fundoplication for treating patients with gastro oesophageal reflux disease concluded that laparoscopic posterior fundoplication (Nissen and Toupet) seemed to provide far more durable and long-lasting relief from reflux symptoms compared to laparoscopic anterior fundoplication (Memon et al., 2015). However, the study design for this meta-analysis was flawed as the authors chose to group together varying degrees of fundoplication into each group, rendering their results invalid (Daud et al., 2015).

1.4.2.4 *Division vs non-division of short gastric vessels*

A randomised trial evaluating late outcomes of division versus no division of short gastric vessels during laparoscopic Nissen fundoplication failed to confer any reduction in side effects at 20 years follow-up (Kinsey-Trotman et al., 2018). Engstrom et al. combined the data sets of a Swedish and Australian study to analyse late outcomes comparing division versus no division of the short gastric vessels during laparoscopic Nissen fundoplication and found no significant differences in post-operative heartburn or dysphagia, ability to belch or vomit, and use of anti-secretory medications. Notably, division of the short gastric vessels was associated with a higher rate of bloating symptoms (Engstrom et al., 2011).

1.4.2.5 *Mesh Vs. No Mesh*

A multi-centre prospective trial by Watson et al. found no significant differences in hiatus hernia recurrence rates for suture + mesh repair compared to suture alone repair at short-term follow-up (12 months) (Watson et al., 2015). The longer-term objective and clinical outcomes from this trial also did not show any advantages for the addition of mesh to a sutured repair of very large hiatus hernias. While these results were consistent with longer term outcomes in a study by Oelschlager et al. which also failed to support the routine use of mesh for the repair of large hiatus hernias, the shorter 6 months follow up had higher hiatus hernia recurrence in suture only group compared to mesh at 24% vs 9% (Oelschlager et al., 2011). Memon et al, in a large, randomised control trial published in 2019, assessed suture repair vs prosthetic repair (non-absorbable and absorbable mesh) for differences in short-term and long-term surgical outcomes after elective laparoscopic hiatus hernia repair. Six outcome variables were analysed including (a) operative time; complication rate; (c) recurrence of hiatus hernia or wrap migration; (d) reoperation; (e) hospital stay; and (f) quality of life (QoL). The authors concluded that mesh hiatal herniorrhaphy may be superior to suture cruroplasty for repair for large hiatal hernias based on a lower risk of revisional surgery and the perception that overall mesh-related complications were extremely low(Memon et al., 2019). Thus, equipoise exists regarding the routine use of mesh for crural reinforcement during laparoscopic repair of large hiatal hernia. Until further high-level evidence emerges in the literature, the use of mesh for reinforcement of hiatus hernia repair should be performed at the discretion of the surgeon.

1.5 Aims

1.5.1 Aim Number 1

To identify all potential pre-operative predictors which may correspond to a successful outcome following a laparoscopic fundoplication based on a narrative review of the literature (manuscripts published between 1995 and 2000).

1.5.2 Aim Number 2

To determine which of the potential predictors identified in Aim #1 were most influential in the occurrence of a successful outcome after fundoplication with a systematic review.

1.5.3 Aim Number 3

To use the best predictors of a successful outcome after fundoplication identified in Aim #2 to interrogate the Flinders Medical Centre's institutional large, prospectively maintained database. For this Aim, a univariate analysis was performed first, followed by regression and machine learning analysis to identify, and validate preoperative variables which are most influential in predicting patient outcomes at 5 years after laparoscopic fundoplication.

2. Choosing the Right Patient for Laparoscopic Fundoplication: A Narrative Review of Preoperative Predictors

2.1 Introduction

Gastro-oesophageal reflux disease (GORD or reflux disease) is defined by the Montreal consensus as a condition that develops when the reflux of gastric content into the oesophagus causes troublesome symptoms or complications (Vakil et al., 2006). According to a review by Nirwan et al., gastro-oesophageal reflux disease has a global prevalence of 14% with significant variations between regions and countries. Whilst the prevalence of reflux disease in Australia and the United Kingdom is 10-15%, the prevalence in the United States of America is higher, at 30-35% (Nirwan et al., 2020). Laparoscopic anti-reflux surgery is an accepted treatment for gastro-oesophageal reflux disease (Anvari and Allen, 2003a, Bammer et al., 2001, Catarci et al., 2004, Dassinger et al., 2004, Lamb et al., 2009a).

However, the published failure rate from laparoscopic fundoplication ranges from 10 to 20% (Zaninotto et al., 2007, Humphries et al., 2013, Morgenthal et al., 2007c), of which 3-6% of patients will require a revisional surgery(Catarci et al., 2004, Dallemagne et al., 2006, Lafullarde et al., 2001, Carlson and Frantzides, 2001, Hunter et al., 1999, Furnee et al., 2009, Smith et al., 2005, Hatch et al., 2004). This small percentage of patients undergoing revisional fundoplication is significant, considering the large number of fundoplications undertaken since the advent of laparoscopic anti-reflux surgery. A revisional fundoplication not only poses a greater technical challenge than a primary fundoplication, but it also results in higher complication rates ranging from 0% - 44% (Symons et al., 2011), and higher risk of mortality (1%) (Iqbal et al., 2006). As well, a further 10% of patients undergoing laparoscopic re-operative anti-reflux surgery may require another revisional procedure (Awais et al., 2011, Deschamps et al., 1997).

Given the risks associated with laparoscopic revisional fundoplication, it is imperative to select the right patient for a primary laparoscopic fundoplication. We aim to determine the best pre-operative predictors which correspond to a successful outcome following laparoscopic fundoplication and will present the article in accordance with the Narrative Review reporting checklist.

2.2 Methods

Gastro-oesophageal reflux disease is one of the most common benign disorders of the upper gastrointestinal tract with non-specific symptoms, heterogeneous clinical presentation, and a varied diagnostic differential. Hence, making the correct diagnosis of reflux, and then making the correct treatment choice (i.e., medical versus surgical therapy) are both of utmost importance.

An extensive literature search was conducted of MEDLINE, Embase, Cochrane and Clinical Key databases using the search terms “fundoplication”, “recurrent reflux”, “predictors of success” with “AND” and “OR” selected. English-written papers published between 2000 to 2020 were included. Abstracts,case reports and studies for patients less than 18 years of age were excluded. Only studies with laparoscopic fundoplication were included, and of those, only studies which focused on *pre-operative* patient predictors or investigations were included. Open, endoscopic and revisional fundoplication studies were excluded, as well as any research paper evaluating hiatus hernia greater than five centimetres in size. Out of a total 431 publications, 83 studies were included in the review after applying the inclusion and exclusion criteria. We derived the following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) flow diagram after applying the guidelines (Figure 2-1).

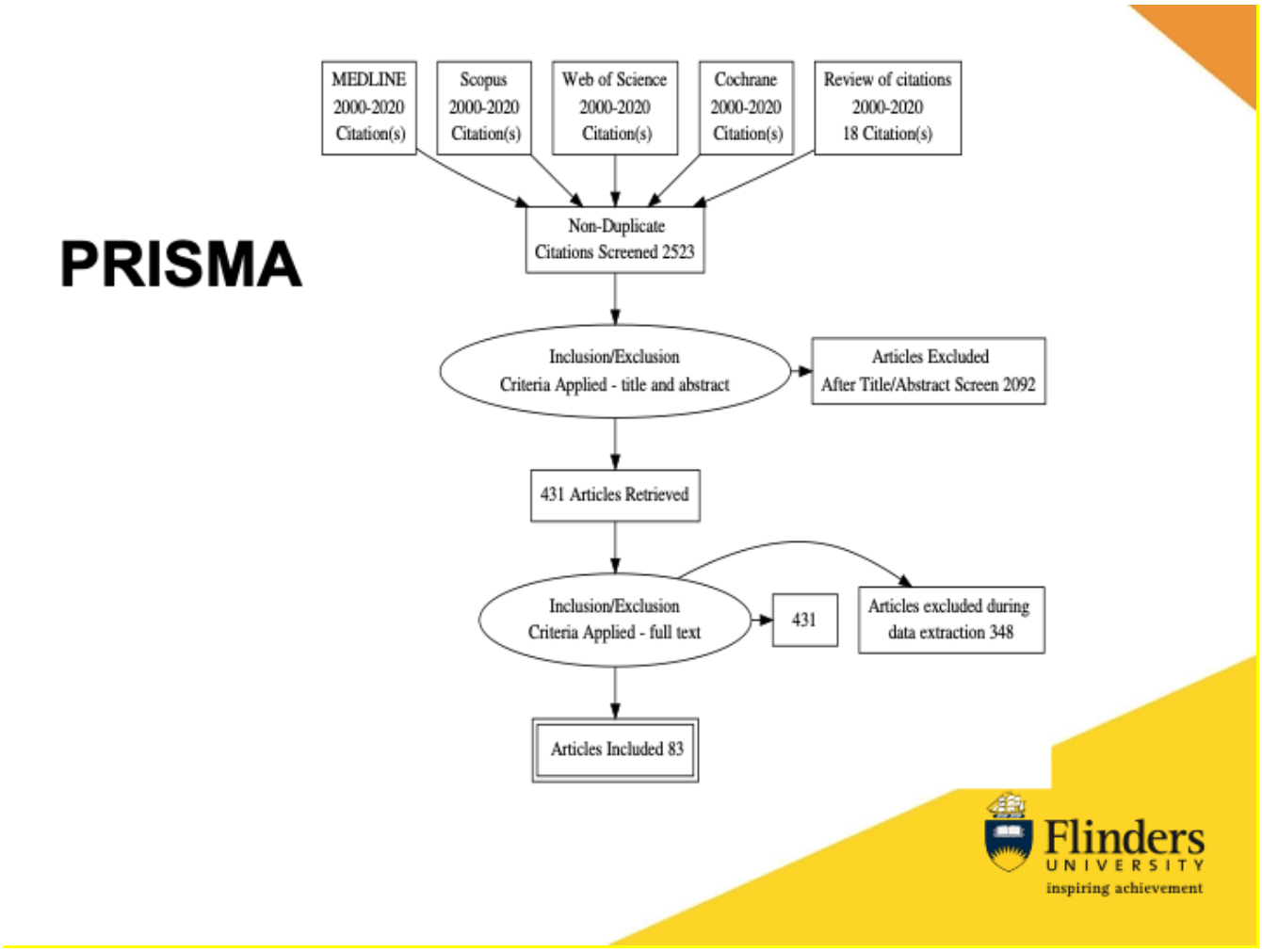


Figure 2-1: Flow diagram PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal. pmed1000097

Forest plots were created as a useful method of synthesizing evidence. A meta-analysis was not undertaken due to wide heterogeneity and varying types of study design.

Further, the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) was applied to evaluate the quality of non-randomized cohort studies (Table 2-1). For randomized cohort studies, Risk of Bias (RoB) 2.0 tool was adopted.

Table 2-1: Risk of bias assessment

Study Name	Confounding	Selection bias	Misclassification	Deviation from intended interventions	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results
Addo 2020	Low - older patients had more morbidity	Low	Low	Low	Low - gradual patient loss to follow-up	Low	Low
Anvari 2003 Response to PPI	Low	Low	Low - tighter wrap in atypical symptom patients	Low	Low - partial follow-up	Low - independent observer	Low
Anvari 2006 BMI	Low	Low	Low	Low	Low	Low – blinding of observer	Low
Beck 2009	Low	Low – only patients with 5 years complete follow-up were selected	Low	Low	Low	Low	Low
Booth 2008	RCT						
Broeders 2009 acid hyper-sensitivity	Low	Low - only patients who participated in the RCT were asked to undergo invasive testing	Low	Low	Low	Low - some patients refused: participate in parts of the post-op protocol	Low
Broeders 2009 #2304 reflux pattern	Low	Low - some patients refused to comply with parts of the post op study protocol	Low	Low	Low	Low	Low
Broeders 2010 ERD vs NERD	Low	Low	Low	Low	Low	Low	Low
Broeders 2011 symptom reflux association	Low	Low/moderate - substantial group of patients were excluded from analysis due to incomplete 24-h pH data	Low	Low	Low	Low - some patients refused parts of post-op study protocol	Low

Table 2-1: Risk of bias assessment

Study Name	Confounding	Selection bias	Misclassification	Deviation from intended interventions	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results
Broeders 2011 #2294	Low	Low	Low	Low	Low	Low	Low
Broeders 2011 #2299	Low/ moderate - Included learning curves	Low	Low	Low	Low	Low/ moderate – wrap was tailored	Low
Brown 2011	Low/ moderate - only a small number of patients reported atypical symptom as primary symptom	Low	Low	Low	Low	Low/ moderate – only LNF included	Low
Chin 2008	Low	Low/ moderate - lack of data on the underlying functional symptoms before surgery in all patients	Low	Low	Low	Low	Low
Chisholm 2009	Low	Low	Low	Low	Low	Low	Low
Cowgill 2006 BE	Low	Low	Low	Low	Low	Low	Low
Cowgill 2006 Age	Low	Low	Low	Low	Low	Low	Low
Cowgill 2007	Low	Low	Low	Low	Low	Low	Low
Del Genio 2008	Low	Low/ moderate – lack of control group	Low	Low	Low	Low	Low
Desai 2003 Oesophagitis	Low - %of women higher in the endoscopy neg group	Low	Low	Low	Low	Low	Low

Table 2-1: Risk of bias assessment

Study Name	Confounding	Selection bias	Misclassification	Deviation from intended interventions	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results
Desai 2003 BE	Low- % males significantly higher in the BE	Low	Low	Low	Low	Low	Low
Fei 2013	Low	Low	Low	Low	Low	Low	Low
Francis 2011	Low	Low – retrospective study	Low	Low	Low	Low	Low
Granderath 2002	Low	Low	Low	Low	Low/moderate only 59.4% at 3 yr follow-up	Low	Low
Hafez 2008	Low	Low	Low	Low	Low	Low	Low
Hamdy 2009 Atypical	Low	Low	Low	Low	Low	Low	Low
Hamdy 2014 Poor response to PPI	Low/ mod - Presence of atypical reflux symptoms in the poor responders	Low	Low	Low	Low	Low	Low
Hong 2004	Low	Low	Low	Low	Low	Low	Low
Jackson 2001	Low	Low	Low	Low	Low	Low	Low
Kamolz 2003 Depression	Low	Low	Low	Low	Low	Low	Low
Kamolz 2005	Low -EGD +ve had higher DeMScore	Low	Low	Low	Low	Low	Low
Kamolz 2003 BE	Low	Low	Low	Low	Low	Low	Low
Kaufman 2006	Low	Low	Low	Low	Low	Low	Low

Table 2-1: Risk of bias assessment

Study Name	Confounding	Selection bias	Misclassification	Deviation from intended interventions	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results
Khajanchee 2009	Low	Low - retrospective	Low	Low	Low	Low/moderate – only 64% had post op pH	Low
Koch 2012	RCT						
Lamb 2009	Low	Low	Low	Low	Low	Low	Low
Lord 2009	Low	Low	Low	Low	Low	Low	Low
Lugaresi 2015	Low	Low	Low	Low	Low	Low	Low
Maret-Ouda 2017	Low/moderate – BMI of patients not known	Low/moderate – no control group, retrospective study	Low	Low	Low	Low	Low
Martin Del Campo2017	Low - class III obesity excluded	Low	Low	Low	Low	Low/ moderate – 54% follow-up	Low
Meneghetti 2008	Low	Low	Low	Low	Low	Low	Low
Miholic 2012	Low	Low	Low	Low	Low	Low	Low
Morrow 2014	Low	Low – no control group	Low	Low	Low	Low - 82% follow-up	Low
Oelschlager 2003	Low	Low – no control group	Low	Low	Low	Low	Low
Park 2019	Low	Low – retrospective, no control group	Low	Low	Low	Low - wrap was tailored	Low
Patti 2002 chest pain	Low	Low	Low	Low	Low	Low	Low
Patti 2003 LES	Low	Low	Low	Low	Low	Low	Low
Pizza 2008	Low	Low	Low	Low	Low	Low	Low
Rakita 2006	Low	Low – no control group	Low	Low	Low	Low	Low

Table 2-1: Risk of bias assessment

Study Name	Confounding	Selection bias	Misclassification	Deviation from intended interventions	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results
Rebecchi 2013	Low - hoarseness and cough more frequently reported in the DGE group	Low	Low	Low	Low	Low	Low
Riedl 2009	Low	Low - only patients with complete pre- & postop data included, retrospective study	Low	Low	Low	Low	Low
Robertson 2017	Low	Low/moderate – only 65% follow-up	Low	Low	Low	Low	Low
Ross 2008	Low	Low – no control group	Low	Low	Low	Low	Low
Rossetti 2014	Low	Low	Low	Low	Low	Low	Low
Sanford 2020	Low	Low - incomplete patient follow-up through 2 years, retrospective study					
Staehelin 2014	Low	Low	Low	Low	Low	Low	
Statz 2017	Low	Low/moderate – poor pre op and post op reporting	Low	Low	Low	Low	Low
Strate 2008	RCT						
Tekin 2012	Low	Low	Low – Toupet more often in obese	Low	Low	Low	Low
Tolone 2013 Age	Low	Low / moderate – poor pre op and post op reporting	Low	Low	Low	Low	Low
Tsuboi 2011	Low	Low/ moderate – retrospective study	Low	Low	Low	Low – data available for only 70% post op	Low

Table 2-1: Risk of bias assessment

Study Name	Confounding	Selection bias	Misclassification	Deviation from intended interventions	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results
Van der Westhuisen 2011	Low - different pre-op work-up	Low – retrospective study	Low	Low	Low	Low	Low
Velanovich 2004	Low	Low	Low	Low	Low	Low	Low
Walle 2019	Low	Low – retrospective study	Low	Low	Low	Low – 57.8% follow-up patients	Low
Wang 2008 Age	Low	Low – retrospective study	Low	Low	Moderate to severe – very low post op follow-up	Low	Low
Wayman 2007	Low	Low	Low	Low	Low	Low	Low
Weltz 2020	Low	Low/moderate – no control group, retrospective study	Low	Low	Low	Low	Low
Wilkerson 2005	Low-more atypical symptoms in poor responders	Low- retrospective study	Low	Low	Low/ mod 71% good & 64% poor responders at 1yr follow-up	Low	Low
Winslow 2002 Reflux patterns	Low	Low	Low	Low	Low	Low	Low
Winslow 2003a	Low/moderate – more smokers and previous and surgery in NSSD	Low	Low	Low	Low	Low	Low

2.3 Discussion

2.3.1 Pre-operative patient predictors

2.3.1.1 *Age*

Age as a predictor of outcome after laparoscopic fundoplication for patients with reflux disease has contradictory findings. Addo et al. in a retrospective study, demonstrated improved long-term quality of life amongst elderly patients undergoing laparoscopic fundoplication, even though the risk of intraoperative complications, length of stay, and re-operation rates were all higher compared to the younger age group (Addo et al., 2021). In a study involving review of a Californian database of 13,050 patients, multivariate analysis demonstrated significantly higher rates of re-operation among younger patients (Hazard ratio, HR = 3.56 for < 30-year-old; Hazard ratio 1.89 for 30–50-year-old; Hazard ratio 1.65 for 50–65-year-old) and female patients (Hazard ratio = 1.35) (Zhou et al., 2015). Older patients had greater symptom improvement, a finding which is consistent across multiple studies (Beck et al., 2009) (Cowgill et al., 2006b) (Pizza et al., 2007).

Large population database studies have also revealed higher rates of re-operation in younger patients compared to patients more than 70 years of age (Zhou et al., 2015) (Obeid et al., 2018). Although a large Swedish study, with up to 5 years follow up, found older age was a risk factor for reflux recurrence (Hazard ratio 1.41 for > 61 years compared to < 45 years). Though the redo fundoplication rate was similar in both groups (2.7% vs 2.6%), the percentage of patients with post laparoscopic fundoplication recurrence treated with medication was higher in the elderly group (19.2%) compared to the younger age group (10.8%) (Maret-Ouda et al., 2017). The Adelaide group reported similar findings noting frequent anti-reflux medication use and re-operation rate (11%) with increasing age (Wijnhoven et al., 2008). In a multivariate analysis, age (<50 years), typical symptoms, and response to proton pump inhibitor pre-operatively had an significant effect on positive outcome after laparoscopic fundoplication compared to outcome for older persons, age > 50 years (Jackson et al., 2001).

2.3.1.2 *Sex*

The likelihood of a successful outcome following laparoscopic fundoplication for women is lower than for men, although most will still have a good outcome. In a large prospectively collected database study, females were less satisfied with the outcomes after fundoplication, consequently having more revisional procedures compared to males (Beck et al., 2009). Observational studies confirm that female sex (odds

ratio 1.56, P<0.0001) is associated with increased risk for re-operation after fundoplication (Zhou et al., 2015) (Obeid et al., 2018). In a Swedish study involving 2,655 patients, the overall recurrence rate of reflux symptoms in female patients was 22% *vs.* 14% in males, and the rate of redo fundoplication was 4% for females vs. 2% for males. Most patients with reflux recurrence were treated with medication at a median follow-up of 5.6 years (Maret-Ouda et al., 2017).

2.3.1.3 *Body Mass Index (BMI)*

Obesity is a recognized risk factor for the development for reflux. Studies evaluating BMI as a predictor for fundoplication outcome have classified patients into 3 categories: BMI <30 kg/m2, ≧30 to <35 kg/m2, and ≧35 kg/m2. While patients with a BMI ≧35 kg/m2 are best suited to bariatric surgery (Mechanick et al., 2013), treatment for moderate obesity (middle BMI group) is more controversial. Poorer outcomes after laparoscopic fundoplication were seen in obese patients in some studies(Perez et al., 2001, Morgenthal et al., 2007a, Hahnloser et al., 2002, Andolfi et al., 2017), whereas other studies found similar outcome regardless of patient BMI (D'Alessio et al., 2005a, Winslow et al., 2003b, Fraser et al., 2001, Campos et al., 1999, Anvari and Bamehriz, 2006, Ng et al., 2007, Chisholm et al., 2009, Tekin et al., 2012). Schietroma et al. compared outcomes for 201 patients based on BMI and found that although short term outcomes were similar for all groups, long term outcomes were not. After more than 10 years, reflux control was worse in the obese group compared to the non-obese group (Schietroma et al., 2017). A recent meta-analysis by Abdelrahman et al. concluded that although laparoscopic fundoplication can be safely performed in an obese patient, higher reflux recurrence is a risk (Abdelrahman et al., 2018). In a study analysing patterns of re-operation for failed fundoplication in 9,462 patients, the majority of patients (86%) underwent conversion to Roux-en-Y gastric bypass were obese, whereas only 8% redo fundoplication patients were obese (Obeid et al., 2018).

2.3.2 Typical vs. atypical symptoms

Laparoscopic fundoplication achieves excellent outcomes in over 90% of patients with gastro-oesophageal reflux disease when associated with typical symptoms, namely heartburn and acid regurgitation (Dallemagne et al., 2006, Morgenthal et al., 2007c, Kaufman et al., 2006, Granderath et al., 2002, Brillantino et al., 2011). However, the effectiveness of anti-reflux surgery for the resolution of atypical symptoms (i.e., cough, hoarseness, globus, odynophagia, sore throat, etc) is less predictive (Kaufman et al., 2006, Iqbal et al., 2008, Lugaresi et al., 2015). Therefore, patients with atypical reflux symptoms should have a concrete diagnosis of pathological reflux through validated objective tests to

qualify for surgery and to elevate the likelihood of good outcome post-surgery. A recent large retrospective study of patients with objectively diagnosed reflux associated with atypical symptoms (difficulty breathing, chronic cough, hoarseness, and globus sensation) and follow up of 19±17 months after laparoscopic anti-reflux surgery, found significant post-operative benefits as assessed by four quality of life validated instruments (Weltz et al., 2021). In the same cohort study, complete resolution of chronic cough was found in 77% of respondents at follow-up (Park et al., 2019).

2.3.3 Response to anti-reflux medication

Most patients with reflux have resolution of reflux symptoms with proton pump inhibitor therapy and are termed as good responders. However, about 17 – 45 % of patients complain of persistent reflux symptoms despite maximal PPI therapy and are deemed poor responders (El-Serag et al., 2010, Donnellan et al., 2005, Becher and El-Serag, 2011, Fass et al., 2005). Patients classified as PPI responders is one of the best predictors for an excellent outcome post laparoscopic fundoplication (Dallemagne et al., 2006, Galmiche et al., 2011), while PPI non responders are considered as poor candidates for laparoscopic anti-reflux surgery. Hence, these patients form an important subgroup of gastro-oesophageal reflux disease patients to be considered for further investigation prior to laparoscopic fundoplication. Studies comparing these two groups, indicate that the non-responders may still benefit from laparoscopic anti-reflux surgery, though not as much as PPI responders (Borie et al., 2014, Hamdy et al., 2014, Wilkerson et al., 2005). Other smaller prospective studies report similar findings, with a fundoplication success rate averaging 85% for PPI non-responders (Brillantino et al., 2011, Antoniou et al., 2008, Frazzoni et al., 2013b).

PPI non responders constitute the most common group of patients referred for laparoscopic fundoplication (Rosenthal et al., 2006, Campos et al., 1999). A systematic review on PPI-refractory GORD patients found that at 10 years post laparoscopic fundoplication, nearly 35% of patients experienced recurrent heartburn, 30% reported regurgitation, and PPI use increased from 9% at 1 year to 18% at 10 years post-surgery. Additionally, 10% of patients with PPI-refractory GORD required surgical intervention within 10 years of follow-up (Hillman et al., 2017). The degree of circumferential extent of fundoplication failed to alter the outcomes for GORD patients refractory to PPI undergoing laparoscopic fundoplication (Lal et al., 2012, Cao et al., 2012, Pessaux et al., 2005). Frazzoni et al. found that for PPI-refractory GORD patients confirmed by impedance pH-study, cure of GORD was achieved in 34 of 38 patients (89%). In 11 patients, abnormal number of total reflux events was the only pre-operative abnormality on

ambulatory impedance-pH testing, suggesting weakly acidic reflux can play a role in the pathogenesis of PPI-refractory GORD (Frazzoni et al., 2013b). In 2018, an expert panel recommended that in PPI-refractory GORD patients undergoing impedance-pH monitoring while on PPI therapy, laparoscopic anti-reflux surgery should only be considered if there is abnormal reflux burden in the form of elevated distal oesophageal acid exposure or regurgitation with positive symptom-reflux association and a large hiatus hernia (Yadlapati et al., 2018). Future studies based on these indications for surgery for PPI-refractory GORD patients may help reduce the burden of revisional fundoplication.

2.3.4 Pre-operative Investigations

2.3.4.1 *Endoscopy*

Patients with reflux are divided into erosive and non-erosive reflux disease based on endoscopy findings. Up to 70% of patients with reflux symptoms have no evidence of oesophagitis at endoscopy (Lind et al., 1997). However, the pre-operative severity of oesophagitis does not influence the outcomes of laparoscopic fundoplication (Watson et al., 1997a, Desai et al., 2003a). Studies comparing the outcomes of patients with or without erosive oesophagitis, found a similar reduction in symptoms and anti-reflux medication use in both groups (Broeders et al., 2010a, Kamolz et al., 2005). However, another comparative study indicated that quality of life outcomes after laparoscopic fundoplication are worse in patients with non-erosive reflux disease, and one third of these patients will continue anti-reflux medication after surgery (Thibault et al., 2006).

Endoscopy remains a vital investigation prior to revisional fundoplication (Iqbal et al., 2008, Jobe et al., 2004). Ideally, it should be undertaken by the operating surgeon as it provides a blueprint for the mechanism of failure and guides management plan (Juhasz et al., 2011).

2.3.4.2 *pH studies*

Ambulatory pH or pH-impedance monitoring is the gold standard for quantifying distal oesophageal acid exposure and establishing a relationship with symptoms in patients with reflux disease(Kahrilas et al., 2008, Richter et al., 2013). In a multivariate analysis conducted by Campos et al. for 199 patients with gastro-oesophageal reflux diseases who underwent a laparoscopic Nissen fundoplication, the strongest predictor for good or excellent outcome was the acid exposure time during 24-hour oesophageal pH monitoring with an odds ratio of 5.4. In contrast, patients with typical symptoms, responsive to anti-reflux medications, but with normal physiological oesophageal reflux/ pH score had only a fair or poor

outcome after surgery (Campos et al., 1999). The value of routine pre-operative oesophageal pH testing was confirmed in another study in which significantly worse subjective outcomes after Nissen fundoplication were found in patients with normal compared with abnormal pre-operative 24-hour pH test results (Khajanchee et al., 2004). In cases of a strong clinical suspicion yet previous negative reflux pH testing, prolonged 48-hour Bravo^{TM} wireless pH monitoring can be considered to improve the diagnostic yield (Penagini et al., 2015, Tseng et al., 2005, Prakash and Clouse, 2005, Pandolfino et al., 2003). The subgroup of patients diagnosed with oesophageal hypersensitivity to acid reflux (i.e., those with a positive symptom association probability, but physiological levels of distal oesophageal acid exposure) are equally good candidates for laparoscopic anti-reflux surgery as patients with pathological acid exposure (Broeders et al., 2009a).

Post-operatively, pH monitoring can also be used to identify fundoplication failures for patients with recurrent symptoms. Oesophageal multichannel intraluminal impedance (MII) monitoring in combination with pH monitoring (MII-pH) in patients either on or off acid suppression medications can detect all types of reflux events (acidic, weakly acidic or non-acidic) recording the retrograde movement of refluxate by impedance and degree of acidity by pH (Agrawal and Castell, 2008). The role of ambulatory impedance monitoring in selecting patients for anti-reflux surgery is evolving. A study by Glasgow et al. urged caution in the use of abnormal impedance values in the context of normal oesophageal acid exposure for the selection of patients for anti-reflux operation. The study found that patients who underwent anti-reflux surgery who had abnormal impedance monitoring but physiologically normal oesophageal acid exposure (DeMeester score <14.7), post-operatively had poor control of heartburn; more frequent new onset dysphagia (23% vs 5%); and significantly more likelihood of continuing proton pump inhibitor therapy after surgery (Glasgow et al., 2020). In a study by Francis et al. of 27 patients with pathological reflux disease but atypical symptoms refractory to inhibitor therapy who underwent laparoscopic fundoplication, predictors of improvement of atypical symptom post-operatively were the presence of heartburn with or without regurgitation concomitant to their primary extra-oesophageal symptom and distal oesophageal pH <4 of more than 12% over 24 hours. The probability of extra-oesophageal symptom improvement was 90% if both conditions were present. Impedance-pH parameters performed on proton pump inhibitor therapy were not predictive of improvement of atypical symptom after fundoplication (Francis et al., 2011).

2.3.4.3 *Manometry*

Oesophageal Motility: Manometric assessment of oesophageal motility is an important investigative tool for pre-operative work-up of gastro-oesophageal reflux disease patients being considered for primary or revisional anti-reflux surgery (Jobe et al., 2013, Patti et al., 2015, Keller, 2018). Abnormalities of motility may contraindicate or modify planned anti-reflux surgery. The importance of undertaking pre-operative manometry is shown by Chan et al., who found 2.5% of 1081 patients referred for anti-reflux surgery had obstructive lower oesophageal sphincter pathophysiology (1% achalasia and 2.5% incomplete LES relaxation) and 4.5% had significant oesophageal body hypomotility, which included aperistalsis in 3.2% and severe hypomotility in 1.3% of patients (Chan et al., 2011). Impaired oesophageal motility is a frequent finding on manometry in patients with reflux disease, however it is not a disease specific finding (Leite et al., 1997) (Tutuian and Castell, 2004, Conchillo et al., 2005, Diener et al., 2001, Lee et al., 2007, Fouad et al., 1999, Smout and Fox, 2012). Tailoring of the fundoplication in patients with ineffective oesophageal motility associated with gastro-oesophageal reflux disease has long been debated, yet several studies show that oesophageal motility does not influence the outcome after laparoscopic anti-reflux surgery (Booth et al., 2002, Cole et al., 2005, Zornig et al., 2002, Munitiz et al., 2004). Randomized controlled trials comparing laparoscopic Nissen vs. Toupet in patients with gastro-oesophageal reflux disease based on oesophageal body motility failed to find any differences in symptomatic outcomes (Booth et al., 2008, Strate et al., 2008). Some patients with gastro-oesophageal reflux disease associated with ineffective oesophageal motility show normalisation of peristalsis and increase in gastro-oesophageal junction pressure after laparoscopic fundoplication (Herbella et al., 2007, Pizza et al., 2008, Tsereteli et al., 2009). A cohort study using a large database comparing the outcomes of 2,040 patients based on the wrap type and pre-operative motility with a follow up of 5 years demonstrated that ineffective oesophageal motility based on conventional manometry did not predict post-operative dysphagia; and tailoring the degree of fundoplication based on pre-operative motility had no impact on long-term postoperative dysphagia (Broeders et al., 2011c). Nevertheless, current common practice is to perform a partial fundoplication in patients with poor pre-operative motility as this yields good post-operative reflux control with high patient satisfaction (Armijo et al., 2019, Liu et al., 2022).

Gastro-oesophageal junction (GOJ): the gastro-oesophageal junction consists of the intrinsic lower oesophageal sphincter pressure and extrinsic crural diaphragm pressure. For many years, manometric

studies reported findings for oesophageal high-pressure zone - failing to recognise the contribution of crural diaphragm pressure. Regardless, many patients with gastro-oesophageal reflux disease show mechanically impaired lower oesophageal sphincter competence with or without low crural diaphragm pressure, in the presence or absence of a hiatus hernia (Cowgill et al., 2007b, Patti et al., 2003, Ritter et al., 1998). Other studies show that normotensive or increased lower oesophageal or gastro-oesophageal junction pressure in patients with reflux disease prior to surgery, has no effect on the outcome after laparoscopic total or partial fundoplication (Morgenthal et al., 2007a, Patti et al., 2003, Riedl et al., 2009, Fibbe et al., 2001, Wills and Hunt, 2001). However, one study with a median follow-up of 14 months (6-81 months) found that patients with a normal lower oesophageal sphincter pressure had a six-fold increase in the risk of developing dysphagia compared to those with an abnormally lowlower oesophageal sphincter pressure (relative risk 5.8) (Blom et al., 2002). A small minority of patients with gastro-oesophageal reflux disease have raised lower oesophageal sphincter pressure. Studies, albeit with smaller samples, have confirmed that this subset of patients have a good outcome after laparoscopic fundoplication (Tamhankar et al., 2003, Varga et al., 2008, Barreca et al., 2002).

2.3.4.4 *Barium Oesophagogram*

Studies to date indicate a limited role for barium oesophagogram (or barium swallow) in the pre-operative work-up of patients with reflux disease (Mittal et al., 2000, Linke et al., 2008). However, the Oesophageal Diagnostic Advisory Panel recommends barium studies in all patients during the work-up for laparoscopic fundoplication (Jobe et al., 2004). Pre-operatively, barium oesophagogram is used to differentiate between a type III paraoesophageal (mixed) hernia and the more common type I sliding hernia, as endoscopy can be inaccurate in this context (Kahrilas, 1999). Barium swallow may identify a foreshortened oesophagus associated with a large (>5cm) hiatus hernia; a non-reducible hiatal hernia (i.e., does not reduce when the patient is upright); and a distal oesophageal stricture.

In symptomatic post fundoplication patients, barium oesophagogram helps with predicting the anatomical cause of a failed fundoplication. It provides information concerning the integrity of the fundoplication, the state of motility, and the presence of reflux in GORD patients with recurrent symptoms post fundoplication (Baker and Einstein, 2014). The role of barium use during fluoroscopic swallow assessment is useful for planning primary or redo fundoplication, as a road map for operative intervention for large hiatal hernia or laparoscopic revisional fundoplication (Dempsey, 2018).

2.4 Conclusion

The table below summarises the findings from the literature review. Best predictors for a good outcome after anti-reflux surgery include male gender, BMI under 30 kg/m2, typical reflux symptoms, responders to anti-reflux medication, and abnormal reflux on 24-hour pH monitoring with positive symptom indices.

Table 2-2 Summary of findings from literature review

Preoperative factors	Predictive strength for a good outcome
1. Age 2. Sex 3. Body mass index 4. Typical vs atypical symptoms 5. Response to anti-reflux medications 6. Endoscopy 7. Reflux test: pH or pH-impedance study 8. Manometry 9. Barium oesophagogram	None Male gender* BMI <30 kg/m²* Typical symptoms*** Good responder*** None Positive pH or pH-impedance study None None
Legend: strength of predictor: *, some evidence; ***, strong evidence	

3. Systematic Review

3.1 Introduction

Laparoscopic fundoplication, first described in 1991 by Tom Geagea has stood the test of time for over three decades and remains the principal treatment for gastro-oesophageal reflux disease (Geagea, 1991). The first decade of laparoscopic fundoplication encountered many challenges, including operator learning curve and technical issues. These were largely resolved through increasing experience and modification to surgical techniques (Gill et al., 2007, Zacharoulis et al., 2006). Today, it is an established gold standard treatment for moderate to severe gastro-oesophageal reflux disease in appropriately selected patients with breakthrough symptoms and/or ongoing oesophagitis, and as an alternative to lifetime medication use.

Despite high success rates following laparoscopic anti-reflux surgery, studies indicate that 10-20% of patients report symptoms consistent with recurrent reflux (e.g., heartburn), or new-onset post fundoplication symptoms (e.g., dysphagia, abdominal bloating, and flatulence) (Bammer et al., 2001). Contemporary reports of recurrent symptoms or post-operative problems show only marginal improvement in recent years (Bammer et al., 2001, Lafullarde et al., 2001, Csendes et al., 2019, Engstrom et al., 2012). This raises the question of what can be done to maximise the chance of a successful outcome for patients after laparoscopic fundoplication?

A study *by Montenovo et al. in* 2009 investigated the use of combined multichannel intraluminal impedance-oesophageal manometry to predict post-operative dysphagia after laparoscopic Nissen fundoplication. They found patients with post-operative dysphagia were significantly more likely to have experienced dysphagia before surgery than not (77 vs. 23%; $P < 0.01$) (Montenovo et al., 2009). These findings raise an important question: prior to surgery, can other pre-operative factors predict a good or bad outcome? The answer may drive best practice pre-operative evaluation for the selection of patients considered suitable for laparoscopic fundoplication and may ultimately improve outcomes post laparoscopic fundoplication. The objective of this research was to identify pre-operative parameters that might be used to predict patient outcome at 1 year or more after laparoscopic fundoplication for gastro-oesophageal reflux disease.

3.2 Material and methods

3.2.1 Literature search strategy

A comprehensive search in Medline, Scopus, Web of science, and Cochrane library databases using terms “anti-reflux surgery OR fundoplication” AND “treatment outcome” AND “post-operative complications” AND “predict OR predictors” for articles published in English from January 2000 to July 2020 was performed. To complete the search, the references of each article were also assessed to identify any additional relevant publications.

3.2.2 Publication and patient selection

Initial screening of title and abstract for all published articles, and subsequent full- text screening was undertaken by two authors (RS, RV)[1]. Discrepancies were resolved by consensus, or independently by a third reviewer (JM)[1]. Inclusion criteria was defined as studies containing both pre-operative predictors and outcomes; studies evaluating individuals aged >18 years; a cohort of more than 100 patients; follow-up of at least 12 months; and primary surgery as laparoscopic fundoplication. Experimental studies, case reports, and duplicate studies were excluded. Studies investigating revisional fundoplication were also excluded.

Note: [1] Co-investigators/ co-authors: RS, R Shukla, MS candidate; RV, R Vissapragada; JM, J Myers

3.2.3 Outcomes of interest

Outcome measures examined included post-operative recurrence of reflux measured subjectively through the reporting of clinical symptoms through validated scoring systems, or objectively, using methods such 24-h ambulatory reflux (pH or pH-impedance) studies, and/or gastroscopy.

3.2.4 Data extraction

A standardised protocol was adopted for all data extraction. The following information was obtained from each published study: 1) general information: study title, first author, year of publication; 2) study characteristics: design, fundoplication type, and duration of follow-up; 3) patient characteristics: number of patients enrolled, preoperative predictor/s; 4) outcome measurements:
symptomatic and objective response.

3.2.5 Quality assessment

The methodological quality of the enrolled papers was assessed using the Risk of Bias in NonRandomized Studies – of Interventions (ROBINS-I) (Sterne et al., 2016) for non-randomized cohort studies. Each study was assessed for bias at pre-intervention stage; for confounding factors and in selection of participants, at intervention; for bias in classification of intervention, and post-intervention; for bias due to deviation from intended interventions, missing data, measurement of outcomes and in selection of the reported result. Based on the criterion, the study was judged to be at low, moderate, serious, or critical risk of bias for all domains.

For randomized cohort studies, Risk of Bias 2.0 (Sterne et al., 2019) was adopted. Formal meta-analysis was attempted but not undertaken due to wide heterogeneity and varying types of study design.

3.3 Results

3.3.1 Age and Gender

A total of nine studies were included to analyse age as a predictor. Five large retrospective comparative studies found statistically significant improvement in subjective outcomes, including postoperative quality of life scores (Addo et al., 2021), DeMeester symptom scores (Cowgill et al., 2006b), modified DeMeester symptom scores (Fei et al., 2013b), Gastrointestinal quality of life or GIQLI (Wang et al., 2008b), and the 36 Item Short Form Survey or SF36 (Tolone et al., 2013) across all ages. Additionally, objective outcomes revealed statistical augmentation in the lower oesophageal sphincter and improvement in peristalsis ($P<0.05$), and significant decrease in 24 hr pH percentage reflux time and DeMeester score at 24 months post-fundoplication in both groups.

However, studies using regression analyses found that increased age (usually ≥ 65 years), was associated with persistence of atypical symptoms after fundoplication (Odds Ratio 1.02, CI 1.01 – 1.04, p=0.013) (Weltz et al., 2021); an increased likelihood of developing more severe dysphagia compared to mild dysphagia (68.2% vs 38.7%, P=0.009) (Walle et al., 2019), and increased post fundoplication use of anti-reflux medications (adjusted hazard ratio 1.41) (Maret-Ouda et al., 2017), (Odds Ratio 1.036, $P<0.001$) (Wijnhoven et al., 2008) or a greater likelihood of revision fundoplication surgery (Odds Ratio 2.36, $p<0.05$).

Three of the four studies analysed sex as predictor, which were larger retrospective database studies and consistently identified poorer outcomes in females compared to males. Females were at higher risk of developing recurrent reflux symptoms (hazard ratio, 1.57; 95% CI, 1.29-1.90); had higher heartburn scores (2.0 ± 2.7 vs. 1.2 ± 2.2; P = 0.0001) and solid food dysphagia scores (2.7 ± 2.9 vs. 2.0 ± 2.5, P = 0.0049); and had elevated symptom scores including DeMeester (2.7 vs. 1.9, P = 0.012) and the modified DeMeester symptom score (3.6 vs. 2.6, P = 0.009). This translated to females reporting lower overall satisfaction with the outcome, a greater use of antisecretory medication (18.4 vs 11.4%) (MaretOuda et al., 2017) and (56% vs 39%) (Robertson et al., 2017), and a higher rate of revisional surgery (3.6 vs 2.2%, HR 1.57; 1.29 – 1.90) (Maret-Ouda et al., 2017) or additional procedures (15.5% vs 8.4%, P = 0.0038) (Beck et al., 2009) following surgery. However, the studies evaluating sex did not report objective outcomes to determine failure.

Key points

- Revisional fundoplication higher in females compared to males 3.6 vs 2.2%.
- Post fundoplication, females have greater need for proton pump inhibitors than males 18.4 vs 11.4%.
- Females have higher risk of recurrent reflux and post fundoplication dysphagia compared to males.

3.3.2 Body Mass Index (BMI)

Six studies were identified which evaluated body mass index (BMI) and its relationship to outcome after laparoscopic fundoplication. Five of the six studies showed good to excellent subjective and objective outcomes after fundoplication in patients with reflux disease across all ranges of BMI (Chisholm et al., 2009, Martin Del Campo et al., 2017, Tekin et al., 2012, Sanford et al., 2020, Winslow et al., 2003b). However, GORD patients with higher BMI (BMI≥30) had a higher mean post-operative reflux symptom score (P<0.0001) (Anvari and Bamehriz, 2006); an increased rate of reflux recurrence (Andolfi et al., 2017, Tekin et al., 2012); but similar Visick I and II scores (Ng et al., 2007) compared to normal and overweight patients. The total number of morbidly obese (BMI≥35kg/m^2) patients with GORD with surgical outcome data was less than 10% (239 out of 3031 patients in the six studies identified) and their outcomes were similar to obese, overweight, and normal weight patients (Chisholm et al., 2009, Sanford et al., 2020, Anvari and Bamehriz, 2006).

Table 3-1 Studies comparing different BMI categories for surgical outcomes

STUDY	SURGERY	OUTCOMES	N	BMI NORMAL/OVERWEIGHT		BMI OBESE	
				<25	25-30	30-35	>35
Anvari 2006	LNF	N Reflux scores/objective	139		69 (50%) Favourable		70 (50%) Favourable
Ng 2007	LNF	N VISICK I & II pH<4 over 4% of time over 24Hr	366	292 (80%) 92% 13/133 (9.8%)		74 (20%) 91% 3/33 (9%)	
Chisholm 2009	LNF or LAF	N Symptom score	481	103 (21%) Favourable	208 (43%) Favourable	115 (24%) Favourable	55 (11%) Favourable
Tekin 2012	LNF 684 or LTF 316	N Recurrence	1000	484 (48%) 3	384 (38%) 14	132 (13%) 3	
Martin Del Campo 2017	LNF	N GERSS GERD HRQL	176	76 (43%) Statistically significant improvement Statistically significant improvement	53 (30%)	47 (27%)	
Sanford 2019	Varied	N Quality of life	869	213 (25%) Favourable across all BMI ranges	323 (37%)	219 (25%)	114 (13%)

LNF, laparoscopic Nissen fundoplication; LAF, laparoscopic anterior fundoplication; AET, acid exposure time (pH<4 over 4% of time during 24-h test postoperatively)

Key points

Compared to normal or overweight category, obese and morbidly obese patients had

- Statistically greater preoperative mean reflux symptom score
- Increased rate of reflux recurrence
- Lower percentage of patients with VISICK I and II

3.3.3 Depression

Comparison using multivariate linear regression analysis of 248 patients with gastro-oesophageal reflux disease of which 88 either had active or past diagnosis of depression, suggested that the presence of depression was an independent predictor of worse quality of life, whereas the absence of depression was associated with better outcomes in terms of quality of life (P=0.02) (Statz et al., 2017). In another study comparing GORD patients with & without depression, significantly higher incidence of chest-pain

(44.7% vs 2.6%), bloating (68.4% vs 18.4%) and dysphagia (50.1% vs 2.6%) were identified after fundoplication, compared to those without depression. Nissen fundoplication had worse symptom outcomes in individuals with depression, compared to Toupet fundoplication with greater chest-pain (82.4% vs 17.6%) and dysphagia (78.9% vs 21.1%). The gastrointestinal quality of life index also remained poor in depressed patients after fundoplication ($P<0.05$) at 1 year after surgery. These findings contrast with the outcomes of objective tests, which identified no differences. Lower oesophageal sphincter pressure and DeMeester score from pH testing remained at normal levels in both groups at 1 year post surgery (Kamolz et al., 2003b), despite symptom differences.

Key points

Compared to non-depressed patients, GORD patients with depression have

- significantly low pre and post gastrointestinal quality of life scores (GIQLI)
- a higher incidence of dysphagia (78.9% vs 21.1%) and chest pain (82.4% vs 17.6%)

Both groups had similar lower oesophageal sphincter pressure and DeMeester scores on pH test revealed physiological normal pH readings after fundoplication

3.3.4 Symptoms

Eleven studies examined symptom type and outcome after fundoplication. The rate of improvement or resolution of gastro-oesophageal reflux disease after fundoplication appeared to be better in patients with typical symptoms (heartburn and regurgitation) compared to atypical symptoms (chronic cough, hoarseness, asthma). The presence of typical symptoms in reflux disease was associated with significantly better outcome after fundoplication (odds ratio 4.3, CI 3.1–10.6, $p<0.01$) as measured by Visick and gastro-oesophageal reflux disease health related quality of life scores. In addition, if presenting symptoms were responsive to proton pump inhibitors (Schindlbeck et al.), the predictive value for a favourable outcome was even greater (Jackson et al., 2001).

Whilst atypical symptoms may improve following fundoplication, the chance of complete resolution is less than 50% (van der Westhuizen et al., 2011, Kaufman et al., 2006, Rakita et al., 2006, Brown et al., 2011, Weltz et al., 2021). The likelihood of resolution of atypical symptoms was also shown to be higher when associated with typical symptoms (88 *vs* 45.5%) than when atypical symptoms were present in isolation (Hamdy et al., 2009). Severe, long standing typical symptoms of reflux disease (pre vs post

operative evaluation, P=0.0001) and percentage of total time at pH<4 in the distal oesophagus (P=0.020) were predictors of improved resolution of chronic cough (achieved in 57 of 67 patients, 85%) (Lugaresi et al., 2015), while heartburn (OR 6.6, P=0.05) and oesophageal pH<4 more than 12% of 24-hour period (OR 10.5, P=0.02) were predictors of a good outcome for atypical symptoms in another study (Francis et al., 2011).

Whilst Patti *et al.* found resolution or improvement in chronic cough (96%) in conjunction with reflux symptoms during 24-hr pH monitoring (Patti et al., 2002), abnormal DeMeester score or the presence of cough on symptom reflux association was not shown to predict post-operative resolution of cough (Park et al., 2019).

Table 3-2 Studies assessing improvement or resolution of symptoms after fundoplication

First Author, Year	Kaufman, 2006	Rakita, 2006	Brown, 2011	Westhuizen, 2011	Weltz, 2020
Cohort (Respondents)	128	322	113	611 (244)	420
Fundoplication type	Nissen (96%)	Nissen (100%)	Nissen (100%)	Nissen (100%)	Nissen (81%)
SYMPTOM	Improved (I, %) or Resolved (R, %)				
	I R	I R	I R	I R	I R
Heartburn	91% 59%		88% 80%	90% 51%	
Regurgitation	92% 72%		87% 83%	93% 59%	
Chest pain		81%	76% 78%		
Dysphagia	75% 57%		96% 66%	84% 43%	
Chronic cough	74% 41%	69%	75% 51%	76% 37%	81%
Hoarseness	66% 42%		74% 46%		66%
Asthma/ wheezing	69% 42%	83%	72% 48%	60% 22%	86%
Sore throat	70% 49%			83% 48%	

I, improved; R, resolved.

3.3.5 Response versus no response to proton pump inhibitors

Three large studies comparing patients with reflux disease who reported a good response to proton pump inhibitors (Schindlbeck et al.) to those with a poor response and found excellent subjective and objective outcomes after Nissen fundoplication, and no difference in outcome for different PPI response groups. Though there was statistical improvement in both groups after surgery, the good responders

had higher satisfaction (94% vs 84%) and better quality of life scores (VISICK I and II 94% vs 87%) (Anvari and Allen, 2003b, Wilkerson et al., 2005, Hamdy et al., 2014). Additionally, three more studies using regression analysis identified that a good response to proton pump inhibitor in patients with reflux disease prior to surgery was statistically the strongest predictor (odds ratio 6.5, CI 4.4-15.2, P<0.001) for a good outcome after fundoplication (Jackson et al., 2001), and non-response to proton pump inhibitor (P<0.001) was a predictor of failure (Power et al., 2004). At multivariate level, the effect is exponentially greater if age ≤ 50 years and typical symptoms are associated with a good response to proton pump inhibitors in patients with reflux disease (Jackson et al., 2001).

Table 3-3 Studies reporting findings for patient response to proton pump inhibitors

STUDY	SURGERY	PR vs GR	OUTCOMES	RESULTS	
Anvari 2003	360 Fundoplication	114 vs 67	Reflux symptom score pH test scores LES tone PCS/MCS	Excellent symptom control but higher scores in PR Within normal limits at 5 years Remained normal at 5 years. Excellent in both; higher in GR	
Wilkerson 2005	360 Fundoplication	91 vs 233	VISICK I or II	87% vs 94% at 1 year	
Hamdy 2014	360 Fundoplication	74 vs 296	Resolution at 1 year of Heartburn Regurgitation Dysphagia Atypical symptoms Patient satisfaction LESP 24Hr pH monitoring	PR 73% 84% 89% 83.9% 84% Excellent Excellent	GR 93% 96% 90% 96.6% 94% Excellent Excellent

PR, Poor Response; GR, Good Response; PCS, Physical health component score; MCS, Mental health component score

3.3.6 Upper Endoscopy

Oesophagitis

Four studies reported outcomes in patients with erosive vs non-erosive reflux disease. GORD patients with erosive reflux disease had higher DeMeester scores on pH studies and a higher incidence of hiatus hernia (Desai et al., 2003a, Lord et al., 2009, Kamolz et al., 2005). Fundoplication resulted in excellent

subjective outcomes including significant reduction in typical and atypical symptoms (Desai et al., 2003a, Lord et al., 2009, Kamolz et al., 2005, Broeders et al., 2010a), higher satisfaction (97% vs 92%) (Desai et al., 2003a), statistical improvement in quality of life (VISICK I and II 89% vs 96%) (Broeders et al., 2010a), and gastro-intestinal quality of life score ($P<0.05$) in non-erosive and erosive reflux disease (Kamolz et al., 2005). The use of anti-reflux medications post fundoplication reduced by 80 vs 83% (Desai et al., 2003a) and by 61 vs 66% (Broeders et al., 2010a) at 5 years in another study. Though at 3 months post-surgery, endoscopy revealed complete healing in 87% (82 of 94 patients) of the erosive group, and development of oesophagitis in 6% (4 of 70) in the non-erosive group (Broeders et al., 2010a), another study reported no signs of oesophagitis at 5 years (Kamolz et al., 2005). The 24-hr pH study parameters including DeMeester score, and lower oesophageal sphincter pressure remained within the normal range in both groups at 5 years (Kamolz et al., 2005, Broeders et al., 2010a).

Table 3-4 Studies reporting various outcomes after fundoplication based on pre-operative endoscopy findings

Studies	Desai 2003	Broeders 2010	Lord 2009	Kamolz 2005
TOTAL (N)	414	213	157	178
Fundoplication	360° & 270° ineffective motility	360°	360°	360°
Group: NERD or ERD	NERD ERD 84 330	NERD ERD 96 117	39 NERD 42 mild ERD 35 severe ER 44 BE	NERD ERD 89 89
Reduction in use of anti-reflux medications	80% vs 83%	61% vs 66%		
Subjective GERD outcomes	Typical and Atypical (p<0.05) pre and post	Relief of reflux symptoms 89% vs 96%	Excellent symptom control in >90% patients	Significant improvement p<0.001-0.05 in all symptoms
Quality of life score improvement		50.3 to 65.2 P<0.001 vs 52 to 60.7 P=0.016		GIQLI score p<0.05 in both groups
Endoscopy at 3 months post fundoplication		87% ERD patients healed oesophagitis vs 6% NERD developed oesophagitis		
Follow up	6 - 109 months	5 years	Mean 36.7 months	5 years

NERD, non-erosive reflux disease; ERD, erosive reflux disease; BO, Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; GIQLI, gastrointestinal quality of life questionnaire

Barrett's oesophagus

Barrett's oesophagus is at the more severe end of the spectrum of reflux. Studies report higher incidence of Barrett's oesophagus in male patients, with higher DeMeester scores, an increased incidence of hiatus hernia, but fewer reflux symptom complaints (Miholic et al., 2012).

Three large comparative studies found excellent but statistically similar improvement and resolution of typical and atypical symptoms (P<0.001) (Desai et al., 2003b), as well as subjective scores such as gastro-intestinal quality of life to normal levels (Kamolz et al., 2003a), and Likert scale (Cowgill et al., 2006a). Post-surgery, there was a 74% reduction in use of anti-reflux medications (P<0.001) and 84% considered their decision to undergo fundoplication to be correct.

Post-fundoplication endoscopy suggested regression of Barrett's oesophagus following fundoplication in 15% with intestinal metaplasia (Desai et al., 2003b), 54% (Oelschlager et al., 2003) and 33% (Morrow et al., 2014) in short segment Barrett's oesophagus. However long-segment Barrett's oesophagus had either minimal (10%) (Morrow et al., 2014) or no evidence of regression in intestinal metaplasia (Oelschlager et al., 2003) at long-term follow-up. Rather, long-segment Barrett's oesophagus was associated with risk of reflux symptom recurrence (RR 6.6; P<0.001) compared to short segment or absent intestinal metaplasia (Miholic et al., 2012). Progression to high-grade dysplasia or adenocarcinoma was identified in one study (7%) (Morrow et al., 2014), though another study did not show evidence of disease advancement (Desai et al., 2003b).

A notable feature was higher rate of anatomic failures (defined as fundoplication disruption, migration, or recurrent hiatal hernia) in Barrett's oesophagus patients (12% vs 5%, P=0.05) (Desai et al., 2003b) and 9% vs 2% in non-Barrett's oesophagus patients (Oelschlager et al., 2003).

Table 3-5 Studies with outcomes comparing Barrett's oesophagus patients

STUDIES	Desai 2003	Oelschlager 2003	Morrow 2014
N	BO=68 vs non-BO=380	106 BO patients	82 BO patients
Fundoplication type	Nissen or Toupet if severe dysmotility	Nissen or Toupet if severe dysmotility	Majority had Nissen (84%)
Reduction in use of antireflux medications %	BO 74% vs Non-BO 79%		
Symptomatic outcomes	Typical and atypical symptoms p<0.001	Improvement or resolution in >80%	Excellent symptom control
Surveillance endoscopy: regression or progression	7/50 (15%) regression of BO with intestinal metaplasia	Complete regression in 30/54 (54%) SSBO. 0/36 (0%) LSBO.	18/82(22%) BO regression 15/46 (33%) SSBO. 3/29 (10%) LSBO, while 6/82 (7%) BO progression (dysplasia or adenocarcinoma)
Anatomic failures for BO vs non-BO	12/68 (18%) vs 5 / 380 (1%)	9% vs 2%	
Follow up	6 months to 7 years	Mean 43 months	Median 8 years (1-16)

BO, Barrett's oesophagus; SSBO, short segment Barrett's oesophagus; LSB, Long segment Barrett's oesophagus

3.3.7 Ambulatory Reflux Study

Positive vs. negative 24hr pH study

A total of nine studies were included comparing pH studies and its various parameters to predict outcomes after fundoplication. Patients with reflux disease and a normal pre-operative DeMeester

score at 24-Hr pH study had higher rates of failure with recurrent typical symptoms, compared to those with abnormal (>14.7) DeMeester scores, according to regression analysis (odds ratio 9.02; P<0.01) (Khajanchee et al., 2004). The risk of reflux symptoms recurrence for DeMeester score ≥ 50 was 23% compared to 9% (P<0.05) for DeMeester score <50 (Hafez et al., 2008). However, a larger study of 481 patients concluded that fundoplication remediates symptoms of reflux, irrespective of the of the DeMeester score (Ross et al., 2008).

Symptom Index and Symptom Association Probability (SAP)

Ambulatory 24hr pH/ pH-impedance reflux studies often utilise two symptom indices for greater diagnostic yield, namely: Symptom Index (SI; a *Positive SI* is defined as >50% reflux related symptoms events as a proportion of all symptom events) and Symptom Association Probability (SAP; the statistical probability or likelihood of symptom-reflux association; *Positive SAP* is defined as >95% probability that symptom events are associated with reflux events i.e., greater than chance alone). To explore the relationship between SI and surgical outcome, a study compared the symptom index for: zero (no symptoms), typical, and atypical symptoms and found statistically similar heartburn and dysphagia scores after fundoplication. Albeit, there was better satisfaction scores in patients with typical SI (zero SI vs typical SI P=0.03 and atypical vs typical SI P=0.02) and better control of heartburn at one year (Chin et al., 2008). Moreover, a multivariate analysis found that a positive SI was associated with better gastro-intestinal reflux disease health related quality of life (GORD-HRQL) and SF-36 quality of life outcomes (P=0.003 vs P=0.274) compared to negative SI<50% at one-year follow-up (Rossetti et al., 2014). The utility of symptom association probability (SAP) in patients with pathological reflux prior to fundoplication and its influence on operative outcome is also worthy of exploration. Patients with a pre-operative positive pH study (i.e. abnormal distal oesophageal reflux) with either negative SAP or positive SAP, had similar outcomes 5 years after surgery with symptom relief (95% vs 87%), reduction of proton pump inhibitor use (55% vs 71%) and improved quality of life (VISICK I or II 95% vs 87%). Objective studies including acid exposure time reduced to 0.2 vs 1.6 with significant reduction in oesophagitis in both groups (P<0.050). There was no difference between groups in terms of likelihood of re-intervention at 6 years post fundoplication (14% and 13%, respectively) (Broeders et al., 2011a). The same authors also reported statistically similar outcomes in patients with positive SAP yet physiological distal oesophageal acid exposure time (oesophageal acid hypersensitivity) and patients with positive SAP and

pathological distal oesophageal acid exposure time, confirming the predictive value of SAP in patients with oesophageal hypersentivity for a good outcome (Broeders et al., 2009a).

Whilst a study categorising percentage time pH<4 in the distal oesophagus during 24hr-pH monitoring into normal <4, mild (4-7) and severe reflux (>7) failed to predict outcomes in terms of heartburn, dysphagia, and satisfaction scores at 1- and 3-year post fundoplication (Staehelin et al., 2014), the above indices and DeMeester score, helped to predict post fundoplication outcomes.

A separate study using multichannel intraluminal impedance pH monitoring (MII-pH) found excellent outcomes (modified DeMeester symptom score) with 98.3% satisfaction rate in patients selected for surgery with either: pH+ (patients with positive pH+ monitoring), pH-MII+ (patients with normal pH monitoring and a positive total number of reflux detected at MII), and pH-MII-SI+ (patients with normal pH monitoring and absence of high number of reflux detected at MII and a positive Symptom Index correlation) at one year follow-up. However, the study did not have a control group and did not use objective evidence of success (del Genio et al., 2008).

Table 3-6 Fundoplication 5yr outcome based on symptom association probability of preop 24h pH

Study: Author, Year	Broeders 2009		Broeders 2011	
Fundoplication type	Nissen		Nissen	
Group, preoperative pH SAP positive or negative	Normal pH SAP +	Abnormal pH SAP +	Abnormal pH SAP +	Abnormal pH SAP -
N	28	126	109	29
Quality of life, VAS 0-100	52 to 69	52 to 64	52 to 74	51 to 75
Visick I or II	85	88	87	95
Post-operative PPI use, %	4%	7%	14%	25%
Change in AET, 24h pH, %	3.9% to 2.6 %	13.2% to 2.3%	13·4% to 1·6%	11·1% to 0·2%*
Oesophagitis, %	In both groups *p<0.001*		44% to 6%	61% to 13%**
Reoperation rate	4/28 (14%)	17/126 (13%)	14%	14%

SAP, Symptom association probability; VAS, visual analogue scale; * $P < 0{\cdot}010$; ** $P < 0{\cdot}050$

PPI, proton pump inhibitor; AET, acid exposure time

Reflux pattern

Eight studies were identified that examined reflux pattern to predict outcomes after fundoplication. For example, reflux occurs commonly after meals, usually when upright. Thus, it is possible the pre-operative patterns of reflux, such as upright, supine, or bi-positional may predict the success of anti-reflux surgery. Three separate studies, where patients were categorised by pre-operative reflux patterns, found similar subjective and objective outcomes post fundoplication (Hong et al., 2004, Cowgill et al., 2007a, Wayman et al., 2007, Meneghetti et al., 2008). Broeders *et al.* findings differed, reporting bi-positional reflux patients presented pre-operatively with more severe disease, and post-operatively showed a higher prevalence of recurrence of oesophagitis and reoperation (Broeders et al., 2009b). However not all studies showed similar design. Power *et al.* looked at predictors of failure rather than success, finding pre-operative abnormal upright reflux pattern predicted failure (Brown et al., 2011).

Abnormal upright reflux was again found to predict less favourable outcome after fundoplication with regards to resolution of typical and atypical GORD symptoms (P<0.05) and lower satisfaction-(P<0.05) compared to the other reflux patterns (Winslow et al., 2002). To illustrate the lack of consistency of findings, a retrospective review found supine reflux pattern was an independent predictor for recurrent pathological reflux (OR 1·03, 1·00 to 1·07; P=0.025) and redo surgery (OR 1·05, 1·01 to 1·08; P =0·006), and the absolute risk of recurrent pathological acid exposure rose to 46% when present with poor oesophageal peristalsis (Broeders et al., 2011b).

Table 3-7 Studies comparing reflux patterns and outcome after laparoscopic fundoplication

Studies	**N**	**Fundo**	**Outcome(s)**	**Upright**	**Supine**	**Bipositional^**
Hong 2004	225	360	Normalised DM score	80.4%	73.3%	75% (p=0.56)
Cowgill 2007	417	360	Would repeat surgery Excellent-good outcomes	84.5% 81%	88.5% 81%	82.6% 73%
Wayman 2007	372	Varied 360, 90 or 180	Subjective and objective Statistical values	Favours surgery	Favours surgery	Favours surgery
Meneghetti 2007	225	360	Subjective and objective Statistical values	Favours surgery	Favours surgery	Favours surgery
Broeders 2009	234	360	VISICK I/II Surgical reintervention after 6 years Recurrent pathological reflux at 5 years	86% 8.9% 10.7%	98% 4.1% 18.8%	95% 20% 40.9%
Winslow 2002	117	360 in majority, some had 270	Favour surgery Global satisfaction Prevalence of typical symptoms after surgery Prevalence of atypical symptoms	77% 88% 18% 45%	97% 98% 8% 30%	98% 90% 15% 15%

^Preoperatively, bi-positional reflux patients had more severe form of acid reflux disease based on 24 hr oesophageal pH testing and oesophagitis on gastroscopy (in all 6 studies).

3.3.8 Manometry

Oesophageal peristalsis and contractile vigour

Eight studies evaluated oesophageal peristalsis and contractile vigour as a predictor of outcomes after fundoplication. Oesophageal dysmotility is a common finding during manometry in patients with gastro-oesophageal reflux disease, and ineffective motility, defined as oesophageal body contraction amplitude <30 mmHg or distal contractile integral <100 mmHg.cm.s and/or non-transmission of peristalsis to the distal oesophagus, is the most common abnormality.

Randomised control trials and retrospective studies comparing outcomes in patients with oesophageal dysmotility and those with normal peristalsis found excellent, and statistically similar post-surgery improvement in typical symptoms ($P<0.001$) (Booth et al., 2008, Granderath et al., 2002, Pizza et al., 2008), as well as atypical symptoms ($P<0.05$) (Granderath et al., 2002, Pizza et al., 2008).

Studies also reported statistical improvement in subjective scores including gastrointestinal quality of life (Granderath et al., 2002), satisfaction (87% vs 83%) (Strate et al., 2008, D'Alessio et al., 2005b), DeMeester symptom scores ($P<0.001$) and VISICK I or II 91% vs 92% (Booth et al., 2008), gastrooesophageal reflux disease health related quality of life ($P<0.0001$) (Velanovich and Mahatme, 2004). However, patients with non-specific spastic motor disorders of oesophagus were found to have increased symptoms of heartburn and regurgitation 25% vs 7% ($P=0.012$), dysphagia 28% vs 14% ($P=0.061$), waterbrash 14%vs 4% ($P<0.05$), and use of anti-reflux medications 5% vs 17% compared to normal motility patients (Winslow et al., 2003a).

The incidence of new onset dysphagia or post fundoplication worsening of dysphagia was similar in effective vs ineffective peristalsis 23% vs 15% $P=0.36$ (Booth et al., 2008), including the incidence of persistent post-fundoplication dysphagia 3.2% (Pizza et al., 2008) and transient dysphagia (Velanovich and Mahatme, 2004, Broeders et al., 2011c) and the need for dilatation or surgery. Regression analysis demonstrated that pre-operative oesophageal peristalsis was a weak predictor for dilatation (odds ratio 1.01; $P=0.041$) and did not predict redo surgery (odds ratio 1.01; $P=0.201$) for dysphagia (Broeders et al., 2011c).

The question of whether a particular fundoplication type would contribute to dysphagia was also investigated. While some studies indicated post-surgery normalization of peristalsis in patients with reflux disease and ineffective peristalsis (up to 84%) and no change post-surgery for those patients with

normal peristalsis (Pizza et al., 2008), others reported either no impact on dysphagia scores (D'Alessio et al., 2005b) or improvement in dysphagia scores in patients with motility disorder after Nissen fundoplication (P<0.0001) (Velanovich and Mahatme, 2004). In contrast, randomised controlled trials report higher dysphagia rates (27 vs 9%; *P* = 0·018) and chest pain on eating (22 vs 5%; *P* = 0·018) at 1 year (Booth et al., 2008), and 19% vs 8%; P<0.05 at 2 years (Strate et al., 2008) in the Nissen group compared to Toupet fundoplication.

A large retrospective study of 2040 patients found that revisional surgery rates were higher after 360°fundoplication compared to 90° or 180° fundoplication for troublesome dysphagia and conversely higher surgical intervention for recurrent reflux symptoms after 90° or 180° compared to 360° fundoplication (Broeders et al., 2011c).

Though ineffective motility does not affect outcomes after fundoplication, the type of wrap may affect the outcome. As evident in some studies, caution should be exercised in operating patients with ineffective motility and wraps should be customised accordingly (Granderath et al., 2002, Velanovich and Mahatme, 2004, Winslow et al., 2003a). This is despite studies reporting that a laparoscopic Nissen fundoplication has no effect on adverse outcomes (Pizza et al., 2008, D'Alessio et al., 2005b).

Key points

- Preoperative oesophageal motility does not affect the outcome after laparoscopic fundoplication, irrespective of the type of wrap.
- Non-specific disorders of the oesophagus discovered on manometry (e.g. spastic motor disorder of the oesophagus) has no influence on the outcomes after fundoplication.

Lower oesophageal sphincter pressure

Four studies explored the influence of lower oesophageal sphincter data from manometry on. Fudnoplication outcome, using incidence of de novo dysphagia as primary outcome failure. GORD patients with pre-operative competent or defective lower oesophageal sphincter (≤ 1 cm intra-abdominal length or < 8 mmHg) or with low (<14 mmHg) or normal (14-24 mmHg) lower oesophageal sphincter resting pressures assessed by conventional manometry, were shown not to affect the fundoplication outcomes, including the rate or frequency of de novo dysphagia (7% in <14 mmHg group

vs 2% in 14-24 mmHg group) (Patti et al., 2003, Riedl et al., 2009). A statistical improvement in typical symptoms (>90%) (Patti et al., 2003) and in subjective scores including GIQLI and HRQL was noted post surgery for ?which patient group (Riedl et al., 2009). Although, another study reported higher incidence (22% vs. 4%) and a relative risk of 5.8 in de novo dysphagia with normal lower oesophageal sphincter (resting pressure 6-26 mm Hg, total length >2 cm, intra-abdominal length >1 cm) compared to abnormal lower oesophageal sphincter (Blom et al., 2002).The study excluded patients with pre-operative dysphagia and had a median follow-up of 14 months (range 6 to 81 months). Further, patients with a hypertensive lower oesophageal sphincter (≥ 30 mmHg end expiration conventional manometry) and higher pre-operative solid dysphagia score were at risk for revisional fundoplication compared to those with low dysphagia score and a hypertensive lower oesophageal sphincter (P=0.036) (Lamb et al., 2009b).

Table 3-8 Studies comparing status of lower oesophageal sphincter (LOS) status on outcomes

Studies	Patti 2002	Riedl 2009	Lamb 2008	Blom 2002
N	280	351	60 well matched out of 1886	163
LOS pressure	Normal LOS Hypotensive LOS	Normal LOS Defective LOS	Hypertensive LOS	Normal LOS High pressure LOS
Fundoplication	Normal peristalsis -Total fundoplication Abnormal peristalsis -Partial fundoplication	Nissen	Nissen 20 in each group, Partial for 10 in each group	Nissen
Follow up	17±22 months	1 year	99 (12-182) months	14 (6-81) months
Outcome	Favors surgery	Favors surgery	Favors surgery, with caution for hypertensive LOS with dysphagia	Risk of dysphagia

LOS, lower oesophageal sphincter

3.3.9 Delayed Gastric Emptying

There were fewer (Haraldstad et al.) studies investigating delayed gastric emptying as a predictor for outcomes after fundoplication. GORD patients with mild to moderate delayed gastric emptying as confirmed by scintigraphy, had no improvement in reflux symptoms or quality of life (gastro-oesophageal reflux disease health related quality of life GORD-HRQL, SF-36, and Reflux Severity Index) and almost 93% required proton pump inhibitor and prokinetic medications at 5 years after Toupet fundoplication. In comparison, patients with normal gastric emptying had statistical improvement in symptoms and quality of life, with only 9.2% on medications at 5 years. The incidence of bloating was statistically low in normal gastric emptying (6.2% vs 83%, $P<0.001$) at 5 years. Compared to patients with normal gastric emptying in whom the mean gastro-oesophageal junction pressure remained significantly increased at 5 years post-surgery ($P<0.001$), it returned to pre-operative value at 5 years in two-thirds of the patients with delayed gastric emptying. Univariate (odds ratio 6.25; 3.48-10.12) and multivariate (4.13; 2.09-11.01) analysis showed delayed gastric emptying, as a significant predictor of pathological reflux (Khajanchee et al., 2009).

Another comparative study reported higher incidence of dyspeptic symptoms including bloating, nausea ($P<0.02$), diarrhoea, hyper-flatulence ($P>0.21$) and abdominal pain ($P=0.002$) amongst GORD patients with delayed gastric emptying diagnosed objectively (Group 1) compared to GORD patients with subjective symptoms of delayed gastric emptying (Group 2) or those with normal gastric emptying (Group 3). Though Group 1 patients with severe delayed gastric emptying (DGE) underwent pyloroplasty in addition to Nissen fundoplication, this was associated with significant post-surgery diarrhoea (25%). Patients with mild to moderate DGE who underwent Nissen fundoplication only, had a high incidence of bloating (25%), hyper-flatulence (62%) and abdominal pain (31%). The study reported complete relief of reflux symptoms including heartburn and regurgitation and no significant differences in incidence of dysphagia (Rebecchi et al., 2013).

Table 3-9 Gastric emptying and outcomes after fundoplication

Study	Khajanchee 2009	Rebecchi 2013
N	(1) DGE symptoms & abnormal GE 63 (2) DGE symptoms & normal GE 78 (3) No symptoms of DGE 418	DGE 42 NGE 146
Fundoplication	Nissen 512 Nissen + pyloroplasty 47/63 (For patients with severe DGE in Grp 1)	Toupet
Follow up	Mean 21 months	5 years
Outcomes	Subjective and objective similar in all three groups	DGE - predictor of recurrent pathological reflux

DGE, delayed gastric emptying, NGE, normal gastric emptying.

3.4 Discussion

This comprehensive systematic review shows that patients with reflux disease should be selected for surgery with objective evidence of reflux, either a positive pH study and/or endoscopic evidence of oesophagitis. Patients should then undergo a fundoplication based on manometry studies, after ruling out major peristaltic disorders. Most studies report subjective (i.e., quality of life or symptom scores) rather than objective outcomes following anti-reflux surgery. The most important factor to consider is patient expectations from the surgery. Important findings of this review are:

1. Age is not a contraindication to anti-reflux surgery. Elderly patients with chronic gastro-oesophageal reflux disease associated with other co-morbidities, may have marginally less benefit after fundoplication, though the magnitude of improvement in symptoms, as well as overall satisfaction is greater in elderly patients compared to the younger group.
2. Females report worse subjective outcome scores compared to males, but this was not reflected in objective parameters / outcomes. This finding could be due to a number of factors, including higher expectations of symptom resolution after surgery, rather than improvement of symptoms post fundoplication. Females are also less tolerant of side-effects of surgery such as increased flatulence and bloating. Nevertheless, the reasons for lower subjective post-surgery outcome in females may be multi-factorial.
3. Studies comparing body mass index (BMI) as predictor of anti-reflux surgery outcome showed only a minor advantage for outcomes of heartburn, dysphagia, or satisfaction for normal or overweight patients compared to obese and morbidly obese patients.
4. Most patients with gastro-oesophageal reflux disease associated with or without depression have similar objective outcomes. However, the subjective outcomes were worse in GORD patients with depression compared to those with no depression after laparoscopic fundoplication, indicating a poor perception of improvement in reflux symptoms in patients with depression.
5. Poor response to proton pump inhibitor therapy priot to anti-reflux surgery requires further investigation of the cause of symptoms other than gastro-oesophageal reflux disease.
6. Patients with or without erosive gastro-oesophageal reflux disease are expected to have similar outcomes post fundoplication.

7. There is equipoise evidence for regression of Barrett's oesophagus after laparoscopic fundoplication, and studies suggest continued ongoing surveillance. Long segment Barrett's oesophagus is a risk factor for high reflux recurrence rate post surgery.
8. Patterns of reflux did not seem to influence the outcomes after laparoscopic fundoplication.
9. Various motility disorders including ineffective motility and non-specific spastic motility disorders of oesophagus did not influence the outcomes after fundoplication.
10. Competent or hypertensive lower oesophageal sphincter pressure in association with pre-operative dysphagia may pre-dispose GORD patients to post-operative dysphagia after fundoplication. Hypotensive or incompetent lower oesophageal sphincter pressure did not affect the surgical outcome.
11. Delayed gastric emptying (mild, moderate, or severe) may be a significant predictor for recurrent pathological reflux after anti-reflux surgery.

There are several limitations and potential criticisms of this review. A meta-analysis was not possible due to heterogeneous outcomes. Most studies were retrospective cohort studies with some randomized and a few non comparative studies. At pre-intervention, ROBINS-I, for assessment of risk of bias revealed that non-randomized studies reduced confounding through statistical analyses to adjust control for the confounders at preintervention stage and selection bias was moderate due to high attrition rate (about 20-30% at 1 year and 40-50% at 3 to 5 years). Though the operative technique of creating a fundoplication varied, a laparoscopic total fundoplication (i.e., Nissen) was the most common operation (about 75%). However, some studies report partial fundoplication for ineffective motility or for female patients, whereas a tighter wrap was created for patients with atypical symptoms. There was low to moderate risk of bias in the post-intervention domains including that due to missing data, in outcome measurement and in selection of reported results. The definition and measurement of reflux recurrence was different in each study creating variability in post-operative outcomes. Other causes of heterogeneity included a lack of stratification in defining inclusion and exclusion criteria, patient demographics, pre-operative symptom severity, non-standardised criteria for selecting patients for fundoplication, inconsistent length of follow-up after surgery and unreported mode of follow-up (in person *vs.* mail *vs.* telephone). These factors added bias or reduced the quality of the studies. As well, there was a lack of long-term follow-up (more than 5 years) in the studies included, and a reliance on subjective data (i.e., quality of life or symptom scores) rather than objective outcomes.

A strength of our study was the inclusion of larger cohorts with at least one year of follow-up. We only included studies with patient recruitment after 1998 to avoid the learning curve and to gather studies for the period from when the laparoscopic procedure was firmly established (for example, the hiatus was routinely closed). Screening studies with risk of bias tools ensured most comparative studies had a low-moderate risk of bias.

Box 3-1. Summary of predictors for outcome following laparoscopic fundoplication.

Predictors of best outcomes	Predictors of worse outcomes	Predictors not well studied
• Male sex • Typical symptoms • Good response to proton pump inhibitors • Pathological reflux/ pH test	• Female sex • Depression • Long segment Barrett's oesophagus • Delayed gastric emptying†	• Delayed gastric emptying† • Reflux patterns • Morbid obesity

† Gastric emptying listed in two columns – worse outcome but low number of studies; thus, more studies needed

Box 3-2. Summary of findings from scoping review.

Predictors that do not affect outcomes	Predictors to choose with caution
• Age • Normal, overweight, and obese • Motility • Normal hypotensive or defective LOS¥ • Grades of oesophagitis • Barrett's oesophagus (except long segment)	• Physiological reflux in the normal range • Atypical symptoms • Poor response to reflux medications • Morbidly obese • Hypertensive LOS, especially if associated with dysphagia.

LOS, lower oesophageal sphincter; ¥ Defective LES refers to separation of the sphincter and crural diaphragm.

3.5 Conclusion

Male sex, typical symptoms, a good response to PPIs, and objective evidence of reflux were the best predictors of a good outcome after laparoscopic fundoplication. By contrast, patients with depression, isolated atypical symptoms, delayed gastric emptying, and long segment Barrett's oesophagus were predictors of less favourable surgical outcomes. These factors should prompt caution and a need for further work-up prior to surgical intervention. The findings of this review support the notion that it is difficult to get a perfect outcome for all patients after laparoscopic fundoplication, but there are some factors which can help predict better outcomes when carefully considered.

4. Machine learning will not replace clinical acumen yet!

ABSTRACT

Background: Laparoscopic fundoplication remains the gold standard treatment for gastro-oesophageal reflux disease (GORD). However, 10% to 20% of patients experience persistent or recurrent symptoms warranting further treatment. Following a narrative review to identify predictors for the best outcome after laparoscopic fundoplication, these potential predictors were tested using a mature prospectively maintained database. ***Methods*****:** The data of 894 consecutive patients who underwent primary laparoscopic fundoplication from 1998 to 2015, was interrogated using regression and machine learning models. Pre-operative factors were assessed for influence on post-operative outcomes: heartburn, dysphagia, and satisfaction scores at a median follow-up of 5 years. ***Results***: Accuracy in predicting heartburn score (range 0-10) assessed using the Root-Mean Square Error (RMSE) was similar for a negative binomial regression model (RMSE=2.39) and for the Least Absolute Shrinkage Support Operator (LASSO) machine learning (ML) model (RMSE=2.34). Multivariate analysis with complete data generated lower error than using mean imputation for missing values. The most predictive variables were sex for heartburn (ß=-1.5; 95%CI=-2.4, -0.6, p<0.001) and dysphagia (ß=-4.7; 95%CI=-8.0, -1.4, p=0.006), and percentage of oesophageal peristalsis for satisfaction (ß=0.6; 95%CI=0.2, 1.1, p=0.009) and dysphagia (ß=-1.9; 95%CI=-3.4, -0.3, p=0.02). ***Conclusion***: Although sex and degree of intact primary peristalsis are significant predictors for outcomes after laparoscopic fundoplication, prediction of individual patient outcome was relatively poor, and a machine learning model provided only marginal improvement in accuracy. Clinical acumen and a discussion with patients to set realistic post-operative expectations cannot be replaced by machine learning algorithms at the present time.

4.1 Introduction

Laparoscopic fundoplication, first described in 1991 by Tom Geagea (Geagea, 1991), has stood the test of time for over three decades and remains the principal surgical treatment for gastro-oesophageal reflux disease (Geagea, 1991, Roman et al., 2017). The first decade of laparoscopic fundoplication encountered many challenges, including operator learning curve and technical issues. These were largely resolved through increasing experience and modification to surgical techniques (Gill et al., 2007, Zacharoulis et al., 2006). Today, it is an established gold standard treatment for moderate to severe GORD in appropriately selected patients with breakthrough symptoms and/or ongoing esophagitis, and as an alternative to lifetime medication use.

Despite high success rates following laparoscopic anti-reflux surgery, studies indicate that 10 to 20% of patients report symptoms consistent with recurrent reflux (e.g. heartburn), or new-onset post-fundoplication symptoms (e.g. dysphagia, abdominal bloating, and flatulence) (Bammer et al., 2001). Contemporary reports of recurrent symptoms or post-operative problems show only marginal improvement in recent years (Bammer et al., 2001, Lafullarde et al., 2001, Csendes et al., 2019, Engstrom et al., 2012). This raises the question of what can be done to maximise the chance of a successful outcome for patients who consent to laparoscopic fundoplication?

Traditional teaching, based on published findings (Campos et al., 1999), stated that three factors could determine a good outcome after laparoscopic fundoplication: 1) an abnormal 24h oesophageal pH study, 2) the presence of a typical reflux symptoms, and 3) a good response to anti-reflux medication. Another paper published from our institutional database findings in 2002, added a few more predictors to this list based on post-operative satisfaction scores, namely: male sex, privately insured, and the presence of a hiatus hernia (O'Boyle et al., 2002). A narrative review performed in 2021 suggests five predictors for success: male sex, body mass index (BMI) under 30 kg/m2, typical reflux symptoms (heartburn and/or volume regurgitation), a good response to anti-reflux medication, and abnormal reflux on a 24h oesophageal pH study with positive symptom indices (Shukla et al., 2021). Using the information gleaned from our comprehensive narrative review, we interrogated our large, prospectively maintained fundoplication database to identify and validate pre-operative variables that can predict patient outcomes at 5 years after laparoscopic fundoplication for GORD.

4.2 Materials and Methods

A prospective database of all GORD patients undergoing laparoscopic fundoplication at the Royal Adelaide Hospital, Flinders Medical Centre, and associated private hospitals in Adelaide, South Australia, was established in 1991 and stored on a secure, password-protected server (FileMaker Pro ver. 11, FileMaker Inc., Santa Clara, CA, USA). The study and database use were approved by the respective institutional research ethics committees.

4.2.1 Patient Selection

The population consisted of 894 patients who underwent laparoscopic fundoplication with reduction of hiatus hernia and closure of crura performed between 1998 and 2015. These dates were chosen to exclude confounders including the initial learning curve from open to laparoscopic fundoplication (1991-1994), and to exclude techniques that did not routinely include cruroplasty (1994-1997). Patients with redo or revisional fundoplication and/or large hiatus hernia (> 5cm) were excluded. Primary inclusion criteria were: follow-up of at least 5-years post fundoplication (or when not available, 6- or 4-years), and objective documentation of reflux disease prior to surgery.

4.2.2 Patient Workup

Indication for surgery was either poorly controlled reflux symptoms on maximal medical therapy, patient preference for surgery in lieu of long-term anti-reflux medication, primary symptom of volume regurgitation, ongoing oesophagitis on maximal medical therapy, and severe manifestations of GORD (e.g. Barrett's oesophagus with low-grade dysplasia, peptic stricture). All patients underwent clinical evaluation before surgery, as well as upper gastrointestinal endoscopy. Oesophageal manometry and 24-hour oesophageal pH monitoring were performed pre-operatively, the latter selectively for patients without endoscopic evidence of oesophagitis and/or patients with atypical symptoms. Barium swallow and gastric scintigraphy (unless evidence of delayed gastric emptying on endoscopy) were not part of routine pre-operative work-up, and therefore not included as pre-operative factors.

4.2.3 Laparoscopic Fundoplication

The technique of laparoscopic fundoplication has been described elsewhere (Jamieson et al., 1994). Essentially, patients were positioned in reverse Trendelenburg position with legs abducted. The surgeon stood between the patient's legs and the assistant on the patient's left side. A total of five trocars were used. Circumferential mobilisation of the oesophagus was performed to obtain adequate length of intra-

abdominal oesophagus (minimum 3cm). Hiatus hernial sac, if present, was dissected from mediastinum, with complete reduction of sac contents into the abdomen. An umbilical tape or pediatric feeding tube was used around oesophago-gastric junction for retraction. The short gastric vessels were not routinely divided. Hiatal defects were repaired using interrupted, permanent, monofilament sutures. A tension-free total or partial fundoplication was created around the lower oesophagus with interrupted permanent sutures. A 52 or 54 Fr bougie was used for calibration of a Nissen fundoplication, and selectively in patients undergoing partial fundoplication.

Post operatively, anti-emetic prophylaxis was routinely administered in the first 24 hours after fundoplication. Our institutional protocol calls for a contrast study on the first post-operative day to detect complications that may require intervention. It also served as quality control. When a problem was identified on the contrast study (e.g. fundoplication too tight), this was rectified with laparoscopic revision prior to discharge. Patients requiring revisional fundoplication were excluded. Patients requiring conversion to open laparotomy were also excluded from the cohort.

4.2.4 Preoperative factors

1. Demographic factors: age, sex, and body mass index (BMI)
2. Patient factors: typical symptoms (heartburn/volume regurgitation), atypical symptoms (cough/hoarseness/odynophagia/dysphagia/halitosis), chest pain, response to anti-reflux medication
3. Investigative factors:
    a. Upper gastrointestinal endoscopy using the Los Angeles grades of oesophagitis (Lundell et al., 1999), presence versus absence of hiatus hernia (small <2cm; medium 2- 5cm);
    b. Twenty-four-hour oesophageal pH study: percentage of time pH<4, total number of reflux episodes, total number of symptom episodes, symptom index.
    c. Oesophageal manometry: distal contractile pressure (product of contraction amplitude, duration of contraction and length of distal oesophageal segment), percentage peristalsis, lower oesophageal sphincter (LOS) or OGJ resting pressure, LOS/ OGJ nadir pressure.

4. Pre-operative symptom scores: Heartburn, dysphagia to liquids, dysphagia to solids.

4.2.5 Post-operative outcome measures

The post-fundoplication outcome measures used for statistical analyses were:

1. ***Heartburn score****: 0 (no symptoms) to 10 (worst symptoms)*
2. Pre-operative versus post-operative difference in heartburn score
3. Dysphagia to liquids score: 0 (no dysphagia) to 10 (worst dysphagia)
4. Dysphagia to solids score: 0 (no dysphagia) to 10 (worst dysphagia)
5. ***Dysphagia*** *using the reversed Dakkak & Bennett score 0 to 45 (where 0= no difficulty in swallowing, and 45= cannot swallow) (Dakkak and Bennett, 1992)*
6. ***Satisfaction score****: 0 (dissatisfied) to 10 (extremely satisfied)*

In addition, patients were asked if they had their time again, whether they would choose surgery (yes or no). The above three post-fundoplication outcome measures bolded and italicized were used for the regression and machine learning analyses. Surgical outcome measures were determined using a clinical questionnaire in outpatient clinics or by post at 5 years. If no response to follow-up at 5 years, either a 6-year or 4-year follow-up was considered (in that order).

4.2.6 Data collection and statistical analysis

SPSS IBM (Statistical SPSS IBM (Statistical Product and Service Solutions, IBM) was used for statistical analysis. The data was cleaned and checked for outliers and missing values. Missing values were subsequently retrieved from patient records of public or private hospitals, or from the Queen Elizabeth Hospital Department of Surgery Oesophageal Function Laboratory.

For each outcome (satisfaction score, dysphagia, and heartburn), univariate analysis was performed initially followed by both regression-based models and machine learning (ML) prediction models. The latter two were utilised to predict individual patient outcome scores based on pre-operative factors as listed above.

Descriptive results were presented as mean with standard deviation or median with range. Normality of outcome variables was checked. For categorical values, we used crosstabs and Chi-square test for statistical significance. For continuous variables, we used mean difference, ANOVA, or T-test to check for statistical significance, as appropriate. A separate univariate analysis was conducted for each of the outcome variables. Variables $P < 0.05$ were considered statistically significant.

For the regression modelling, negative binomial regression was selected since each outcome data had a non-normal distribution, could be treated as a count-type variable, and were over-dispersed (data variation higher than expected). For each outcome, three different approaches to the regression modelling were trialled, using either all available predictor variables; backward stepwise selection of variables based on statistical significance of variables ($p<0.20$); or a null model (unbiased no predictor variables). For the ML algorithms, four types of common machine-learning regression-based algorithms were utilised: decision tree; random forest; support vector regressor and LASSO (least-absolute shrinkage selection operator).

To ensure reliable measures of accuracy, the study data (n=894) was randomly divided into two separate datasets in a 70:30 ratio, with one dataset used for model training and one used for model testing. This provided N=625 subjects for the training data and N=269 for the test data. Of the 894 subjects, only N=221 subjects had complete data for all variables (N=161 for training data and N=60 for the testing data). We therefore performed two separate analyses for both the training and testing data. Thus, ML analysis was undertaken for subjects with complete data, and another analysis was undertaken for data with imputed values (median value imputation for each variable) for subjects with any missing data.

The accuracy of all models (regression and machine learning) was assessed using the root-mean squared error (RMSE), which is used to reflect the average difference between observed and predicted values. A lower RMSE value indicates better accuracy of the prediction model. The influence of the predictor variables was determined using the p-values for the regression-based models and using the relative feature importance for the random forest models. Feature importance is a common way to describe the influence of variables for tree-based ML algorithms and is calculated by measuring the degree of reduction in the algorithm's loss function (difference between observed and expected values) for each feature (i.e. variable).

Results are presented as line plots for the RMSE, regression coefficients with p-values and 95% confidence intervals for the regression models, and feature importance plots for the random forest ML algorithm.

4.3 Results

4.3.1 Patients

A total of 894 patients were included with a median follow up of 5 years (mean 4.95 +/- 0.3). The mean age was 50 years (SD 13.4) and 52.2% were females. The mean BMI was 29.1 kg/m2 (SD 5.68). Typical symptoms (heartburn and/or regurgitation) were present in 92% of the cohort, and atypical symptoms in 15.6%. Chest pain was present in 11.6%, and the most common indication for laparoscopic fundoplication was poor response to anti-reflux medication (87%).

Endoscopy findings were available for 764 patients, of which 39% of patients included in our study did not have oesophagitis at the time of pre-operative work-up, whilst 21.0%, 19.0%, and 5.1% had Grade B, C or D oesophagitis, respectively. One hundred and six patients had Barrett's oesophagus with intestinal metaplasia (13.9%), and fifteen patients had an oesophageal stricture (2.0%). Three hundred and forty patients did not have a hiatus hernia noted at the time of operation (38%), whilst 241 patients had a small hiatus hernia < 2cm (26.9%), and 166 patients had a medium-sized 2 to 5cm hiatus hernia (18.5%).

Eighty-two percent of patients in our study had follow-up results at the 5-year mark, whilst 85 patients returned their questionnaire at 6 years post-fundoplication, and the remaining 75 patients at the 4year mark. When asked if they made the right decision in having a laparoscopic fundoplication, an overwhelming 775 patients (86.6%) said 'yes'.

4.3.2 Univariate analysis

A univariate analysis was run for each possible post-fundoplication outcome measure (**Tables 1 – 6**), as listed in the Methods section.

Table 4-1 Heartburn score

	Post Heart Burn				Multivariate analysis	
Factors	N	Mean (SD)	T/ Chisquare/F/r	P value	ß value	F value and P value
Age	894		r=0.06	0.07	0.7	0.28
Gender					<0.001	0.025
Male	426	1.43 (2.3)	t=-5.89	<0.001	0.87	
Female	464	2.45 (2.8)				
BMI	890		r=-0.06	0.17		
Typical Symptoms					0.84	0.24
Yes	819	2.0 (2.6)	t=2.79	0.009		
No	25	0.92 (1.9)				
Atypical symptoms						
Yes	140	2.3 (2.7)	t=1.6	0.14		
No	703	1.9 (2.6)				
Chest Pain					0.08	0.8
Yes	102	2.3 (2.9)	t=1.3	0.035		
No	741	1.9 (2.5)				
Surg indication					0.45	0.82
Good	80	1.51 (2.3)	F=2.94	0.03		
Poor	344	1.95 (2.6)				
Regurgitation	257	2.28 (2,8)				
ENT	19	1.00 (2.1)				
LA grade						
No	297	2.16 (2.6)	F = 1.81	0.108		
B	160	2.8 (2.6)				

C	145	1.67 (2.4)				
D	39	1.8 (2.8)				
Stricture	15	0.73 (1.5)				
BE	105	1.6 (2.3)				
Hiatus hernia						
No	338	2.02 (2.53)	F = 1.02	0.36		
Small	246	1.74 (2.5)				
Medium	166	2 (2.7)				
Percentage pH	527		r = 0.037	0.397		
No. of episodes	465		r = -0.069	0.139		
Total symptoms	328		r = 0.075	0.177		
Symptom with reflux	328		r = 0.060	0.281		
Symptom index	328		r = -0.139*	0.012		0.09
Distal contract pressure	582		r = 0.046	0.271		
Percentage peristalsis	775		r = -0.092*	0.011	0.04	0.01
LOS / OGJ rest pressure	777		r = 0.032	0.373		
LOS nadir	768		r = 0.059	0.103		

Male sex, a positive symptom index on 24h pH study, and adequate percentage of oesophageal peristalsis were associated with significant improvement in heartburn scores post-operatively on univariate analysis. On multivariate analysis, only male sex (P=0.02) and percentage of oesophageal peristalsis (p=0.01) predicted postoperative heartburn.

Table 4-2 Difference in heartburn score

	Univariate				Multi variate	
Factors	N (%)	Mean (SD)	Statistic: T/ Chisquare/F/r	P value	ß value	P value
Age	829		r = -0.105**	0.002	-0.02	0.02
Gender						
Male	393	6.2 (3.7)	t=1.8	0.86		
Female	436	5.7 (3.6)				
BMI	599		r = 0.032	0.433		
Typical Symptoms						
Yes	766	6.1 (3.6)	t=3.33	0.001	Ref	
No	24	2.6 (5.0)			2.8	0.2
Atypical symptoms						
Yes	132	5 (4)	t=-3.1	0.19	Ref	
No	658	6.2 (3.6)			-0.07	0.8
Chest Pain						
Yes	100	5.1 (3.5)	t=-2.6	0.75		
No	690	6.1 (3.7)				
Surg indication					0.05	0.9
Good	76	5.9 (3.8)	F = 6.6	<0.001	0.2	0.6
Poor	311	6.4 (3.4)			-0.4	0.2
Regurgitation	246	5.9 (3.5)			Ref	
ENT	18	2.6 (5)			-0.3	0.9
LA grade					-0.3	0.4
No	279	5.5 (3.6)	F = 1.72	0.12	Ref	
B	145	6.2 (3.8)			0.5	0.2
C	133	6.4 (3.7)			0.02	0.9
D	37	6.2 (3.6)			-0.3	0.7
Stricture	14	5.6 (4.1)			-1.1	0.4
BE	102	6.4 (3.3)			0.8	0.1
Hiatus hernia						
No	313	5.8 (3.6	F = 1.05	0.35		
Small	235	6.3 (3.6)				
Medium	153	6.1 (3.7)				

Percentage pH	494		r = 0.041	0.359		
No. of episodes	438		r = 0.089	0.064	0.4	0.4
Total symptoms	314		r = 0.069	0.225		
Symptom with reflux	314		r = 0.132*	0.019	-0.02	0.05
Symptom index	314		r = 0.158**	0.005	0.01	0.01
Distal contract pressure	548		r = -0.062	0.148	-0.005	0.2
Percentage peristalsis	723		r = 0.052	0.162	0.01	0.007
LOS / OGJ rest pressure	725		r = -0.078*	0.035	0.01	0.6
LOS nadir	717		r = -0.081*	0.029	-0.1	0.1

Based on Pearson's correlation, increasing age correlated with less reduction in heartburn (after fundoplication), whereas symptom index had a positive correlation in the improvement of heartburn.

On multivariate analysis, younger patients, higher symptom index, and greater percentage of oesophageal peristalsis predicted significantly higher differences in post-operative heartburn scores.

Table 4-3 Dysphagia to liquid score

	Univariate analysis				Multivariate	
Factors	N (%)	Mean (SD)	T/ Chisquare/F/r	P value	ß value	F or P value
Age	894		r = 0.03	0.4		
Gender						
Male	427	0.9 (1.9)	t=-2.6	<0.001	ref	
Female	465	1.2 (2.1)			0.2	0.3
BMI	892		r = -0.002	0.96		
Typical Symptoms						
Yes	821	1.1 (2.0)	t=2.7	0.01	ref	
No	25	0.4 (1.0)			-0.7	0.7
Atypical symptoms						
Yes	140	1.0 (1.7)	t=-0.44	0.27		
No	705	1.1 (2.0)				
Chest Pain						
Yes	102	0.9 (2.1)	t=-0.73	0.39		
No	743	1.1 (2.0)				
Surg indication					-0.2	0.5
Good	80	0.78 (1.3)	F = 2.23	0.08	-0.7	0.09
Poor	345	0.98 (1.9)			-0.7	0.01
Regurgitation	258	1.3 (2.2)			ref	
ENT	19	0.63 (1.2)			-0.8	0.6
LA grade					-0.13	0.7
No	298	1.3 (2.3)	F = 2.4	0.03	ref	
B	160	0.7 (1.5)			-0.05	0.8
C	145	1.2 (2.2)			0.3	0.4
D	39	1 (2)			0.2	0.6
Stricture	15	1.4 (1.8)			0.7	0.5
BE	106	0.83 (1.7)			0.06	0.8
Hiatus hernia						
No	340	1.2 (2.2)	F = 0.67	0.5		
Small	246	1 (1.8)				
Medium	166	1 (2)				

Percentage pH	892		r = -0.03	0.43		
No. of episodes	892		r = -0.02	0.6		
Total symptoms	892		r = 0.04	0.5		
Symptom with reflux	892		r = -0.009	0.88		
Symptom index	892		r = -0.14*	0.013	-0.005	0.2
Distal contract pressure	892		r = 0.098*	0.018	-0.001	0.7
Percentage peristalsis	892		r = 0.003	0.93		
LOS / OGJ rest pressure	892		r = 0.049	0.168	-0.001	0.9
LOS nadir	892		r = 0.083*	0.021	0.1	0.04

Table 4-4 Dysphagia to solid score

	Univariate analysis				Multivariate	
Factors	N (%)	Mean (SD)	T/ Chisquare/F/r	P value	ß value	P value
Age	892		r = -0.005	0.892		
Gender						
Male	427	1.7 (2.4)	t=-5.5	<0.001	ref	
Female	465	2.7 (2.7)			0.5	0.002
BMI	634		r = -0.007	0.869		
Typical Symptoms						
Yes	821	2.2 (2.6)	t=1.6	0.07	ref	
No	25	1.6 (1.8)			-0.5	0.5
Atypical symptoms						
Yes	140	2 (2.5)	t=-0.9	0.37		
No	705	2.2 (2.6)				
Chest Pain						
Yes	102	2.3 (2.8)	t=0.34	0.29		
No	743	2.2 (2.6)				
Surg indication					-0.2	0.3
Good	80	1.5 (2.3)	F = 2.73	0.04	-0.2	0.04
Poor	345	2.2 (2.6)			-0.1	0.2
Regurgitation	258	2.4 (2.7)			ref	
ENT	19	1.6 (2)			-0.1	0.9
LA grade					0.2	0.3
No	298	2.3 (2.8)	F = 1.46	0.19	ref	
B	160	2.1 (2.4)			0.05	0.8
C	145	2.4 (2.8)			0.3	0.2
D	39	1.7 (2.1)			-0.3	0.4
Stricture	15	2.7 (2.9)			0.7	0.2
BE	106	1.7 (2.2)			-0.2	0.4
Hiatus hernia						
No	340	2.3 (2.7)	F = 0.54	0.57		
Small	246	2.2 (2.6)				
Medium	166	2 (2.5)				

Percentage pH	527		r = 0.018	0.682		
No. of episodes	465		r = -0.047	0.317		
Total symptoms	328		r = 0.029	0.601		
Symptom with reflux	328		r = 0.018	0.751		
Symptom index	328		r = -0.061	0.274		
Distal contract pressure	584		r = 0.045	0.278		
Percentage peristalsis	777		r = -0.023	0.514		
LOS / OGJ rest pressure	779		r = 0.022	0.541		
LOS nadir	770		r = 0.009	0.805		

Table 4-5 Dakkak dysphagia score

	Univariate				Multivariate	
Factors	N (%)	Mean (SD)	T/ Chisquare/F/r	P value	ß value	P value
Age	866		r = -0.014	0.692		
Gender						
Male	415	7.3 (9.6)	t=-6.2	0.02	ref	
Female	451	11.5 (10.3)			3.5	0.003
BMI	613		r = -0.011	0.786		
Typical Symptoms						
Yes	796	9.4 (10.2)	t=0.57	0.34		
No	24	8.2 (9.5)				
Atypical symptoms						
Yes	135	8.2 (9.9)	t=-1.4	0.28		
No	684	9.5 (10.2)				
Chest Pain						
Yes	102	9.3 (10.1)	t=-0.05	0.9		
No	717	9.3 (10.2)				
Surg indication						
Good	79	7.9 (9.6)	F = 0.7	0.54		
Poor	334	9.6 (10.3)				
Regurgitation	245	9.8 (10.3)				
ENT	18	9 (10.3)				
LA grade					1.7	0.2
No	285	9.7 (10.7)	F = 2.4	0.03	ref	
B	159	8.9 (9.1)			1.4	0.3
C	144	10.5 (10.8)			1	0.6
D	38	8.1 (10.4)			2.3	0.4
Stricture	15	11.6 (10.3)			1.7	0.7
BE	96	6.4 (7.9)			-2.9	0.2
Hiatus hernia						
No	329	9.6 (10.3)	F = 0.57	0.56		
Small	237	9.5 (10.1)				
Medium	160	8.6 (9.8)				

Percentage pH	509		r = 0.035	0.431		
No. of episodes	450		r = -0.036	0.446		
Total symptoms	321		r = 0.079	0.159	0.1	0.1
Symptom with reflux	321		r = 0.038	0.501		
Symptom index	321		r = -0.074	0.189	0.8	0.8
Distal contract pressure	568		r = 0.031	0.460		
Percentage peristalsis	754		r = -0.039	0.289		
LOS/ OGJ rest pressure	756		r = 0.042	0.251		
LOS nadir	748		r = -0.003	0.939		

Females had a higher predilection for dysphagia to liquids, dysphagia to solids, and a higher Dakkak score, postoperatively, compared to males. While a higher symptom index correlated to a reduced risk of dysphagia to liquids postoperatively, a higher distal esophageal contractile pressure and a higher lower esophageal nadir pressure corresponded to higher dysphagia to liquids postoperatively.

Table 4-6 Satisfaction score

	Univariate analysis				Multivariate	
Factors	N (%)	Mean (SD)	T/ Chisquare/F/r	P value	ß value	P value
Age	889		r = -0.014	0.687		
Gender						
Male	425	8 (2.8)	t=1.6	0.93		
Female	464	7.6 (2.7)				
BMI	632		r = 0.02	0.615		
Typical Symptoms						
Yes	818	7.8 (2.7)	t=0.03	0.59		
No	25	7.8 (2.6)				
Atypical symptoms						
Yes	139	7.7 (2.6)	t=-0.5	0.88		
No	703	7.8 (2.8)				
Chest Pain						
Yes	103	7 (3.1)	t=-2.7	0.002	ref	
No	739	7.9 (2.7)			0.6	0.2
Surg indication						
Good	80	8.1 (2.4)	F = 0.64	0.58		
Poor	343	7.8 (2.6)				
Regurgitation	257	7.8 (2.8)				
ENT	19	7.2 (2.8)				
LA grade					-0.3	0.6
No	298	7.5 (3)	F = 2.5	0.02	ref	
B	160	8.1 (2.7)			0.6	0.2
C	143	7.9 (2.7)			-0.1	0.8
D	39	8.4 (2.2)			1.3	0.1
Stricture	15	6.8 (3)			-2.7	0.1
BE	106	8.3 (2.3)			0.1	0.8
Hiatus hernia					-0.5	0.5
No	340	7.6 (2.8)	F = 2.59	0.07	-0.8	0.07
Small	246	8.1 (2.5)			ref	
Medium	164	7.9 (2.9)			-1.2	0.03

Percentage pH	527		r = -0.02	0.64		
No. of episodes	465		r = 0.08	0.086	0.005	0.2
Total symptoms	328		r = -0.015	0.786		
Symptom with reflux	328		r = 0.015	0.790		
Symptom index	328		r = 0.102	0.065	0.008	0.3
Distal contract pressure	582		r = -0.063	0.129	0.000	0.9
Percentage peristalsis	774		r = 0.046	0.201	0.01	0.03
LOS / OGJ rest pressure	778		r = -0.058	0.109	-0.02	0.3
LOS nadir	769		r = 0.029	0.424		

Overall, the presence of a medium-sized hiatus hernia (3-5cm) led to lower satisfaction scores, whereas increased percentage peristalsis predicted better satisfaction after fundoplication. A summary of the univariate findings is shown in **Table 7**.

Table 4-7 Potential pre-operative predictors versus post fundoplication outcome

	Heartburn		Resolution of heartburn		Dysphagia to liquids		Dysphagia to solids		Dakkak score		Satisfaction	
Age	0.07	0.28	**0.002***	**0.02***								
Male vs Female	**<0.001***	**<0.001***	0.86	NA	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**0.02***	**0.003***	0.93	
Heartburn severity	**0.001***	0.3	**<0.001***	**<0.001***	0.11	0.67	0.18	0.8	0.06	0.2	0.2	0.5
Dysphagia liquids	**<0.001***	0.7	0.18	0.9	**<0.001***	0.56	**<0.001***	**0.001***	**<0.001***	**0.02***	0.1	0.5
Dysphagia solids	**<0.001***	0.9	0.7	NA	**<0.001***	**0.003**	**<0.001***	0.6	**<0.001***	0.7	0.2	0.8
Oesophageal Stricture	0.1		0.1		**0.03***		0.1	0.2	**0.03***	0.7	**0.02***	0.1
Hiatus hernia	0.36		0.35		0.5		0.5		0.5		0.07	**0.03***
Symptom Index	**0.01***	0.09	**0.005***	**0.01***	0.5		0.27		0.18	0.8	0.06	0.3
Oesophageal peristalsis	**0.01***	**0.01***	0.16	**0.007***	0.93		0.5		0.28		0.2	**0.03***

4.3.3 Regression and Machine Learning Models

Sex was the most influential predictor, followed by percentage of primary peristalsis. This is shown in a feature importance plot where male sex was the most significant independent predictor for a good outcome after fundoplication, using heartburn score as the primary outcome measure (Figure 4.1). Sex was also a significant predictor when assessing dysphagia score as the primary outcome measure, whilst percentage of primary peristalsis at pre-operative manometry predicted satisfaction score as the primary outcome measure (Table 8).

Imputed full train database **Non missing train database**

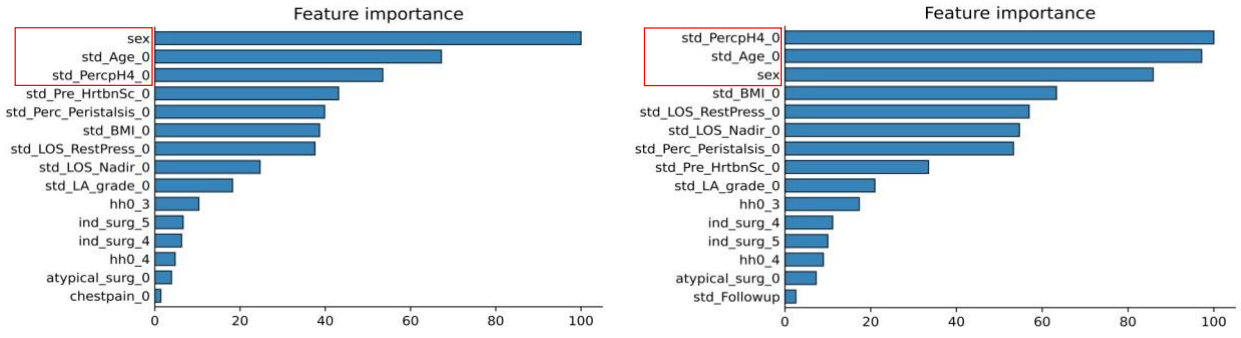


Figure 4.1. Feature importance bar for heartburn

Table 4-8 Regression model for heartburn, dysphagia, and satisfaction scores

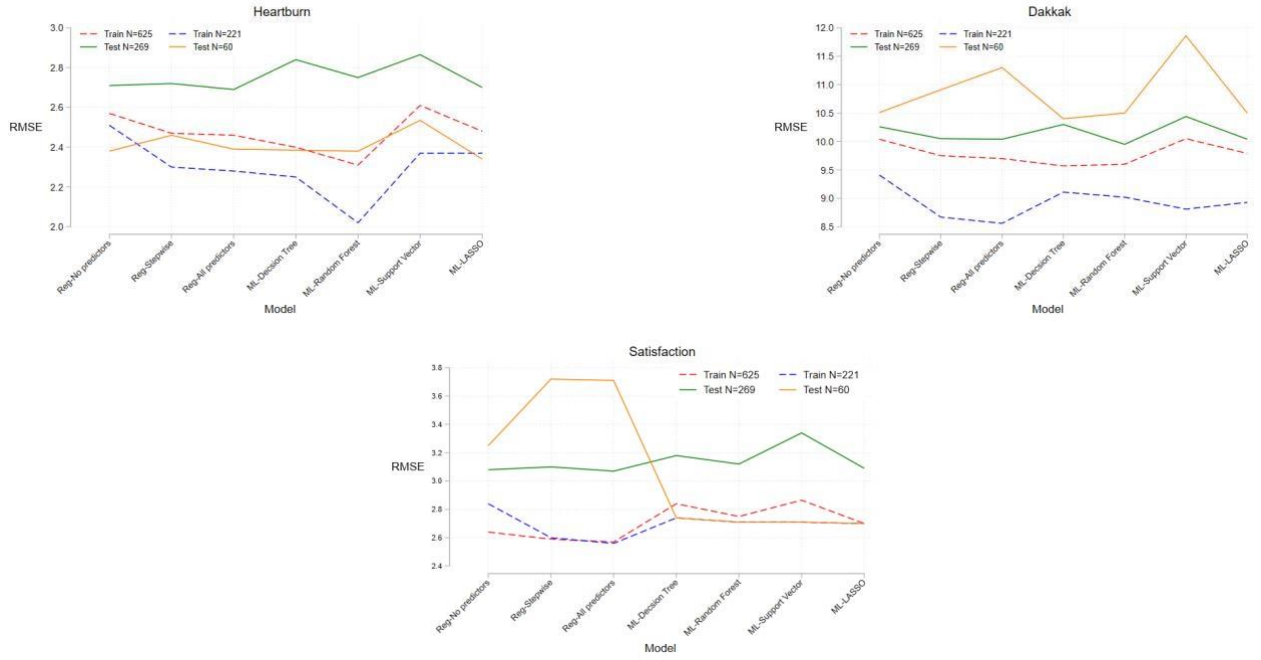
Using the training set (n=625) using all variables (i.e. potential predictors), and the non-missing training set (n=161).

	Imputed train (n = 625)			Non missing train (n = 161)		
	p value and 95% Confidence Interval			*p* value and 95% Confidence Interval		
	Heartburn	Dysphagia	Satisfaction	Heartburn	Dysphagia	Satisfaction
Age	0.22, [0.04, 0.2]	-0.66, [0.51, -1.11]	0.55, [-0.28, 0.15]	0.16, [-0.12, 0.71]	0.78, [-1.7, 1.3]	0.16, [-0.8, 0.13]
Sex	**0.0, [-0.84, -0.34]***	**0.0, [-5.9, -2.5]***	0.09, [-0.07, 0.81]	**<0.001, [-0.23, -0.59]***	**<0.006, [-8.0, -1.3]***	0.08, [-0.12, 1.85]
BMI	0.46, [-0.18, 0.08]	-0.54, [0.58, -1]	0.19, [-0.07, 0.35]	0.28, [-0.64, 0.19]	0.526, [-2,1]	0.241, [-0.18, 0.74]
Typical symptoms	0.46, [-1, 2.22]	0.85, [-11, 9.1]	0.21, [-4.3, 0.99]	0.92, [-4.7, 5.2]	0.62, [-23.4,14]	0.33, [-8.3, 2.8]
Atypical symptoms	0.15, [-0.07, 0.48]	0.24, [-3.1, 0.79]	0.87, [-0.47, 0.55]	0.62, [-1.2, 0.78]	0.762, [-3.3, 4.5]	0.87, [-1.26, 1]
Chest pain	0.4, [-0.21, 0.53]	0.55, [-3.3, 1.77]	0.44, [-0.93, 0.41]	0.6, [-2.1, 1.2]	0.94, [-6.6, 6.2]	0.29, [-0.91, 2.9]
Preoperative heartburn score	0.2, [-0.04, 0.2]	0.41, [-0.48, 1.17]	0.2, [-0.07, 0.36]	0.96, [-0.41, 0.43]	0.33, [-2.4, 0.82]	0.08, [-0.05, 0.9]
Indication for surgery regurgitation	0.73, [-1.5, 2.2]	0.9, [-12.3, 10.8]	0.2, [-1, 5]	0.35, [-3.1, 8.7]	0.3, [-12.6, 31]	0.36, [-3.6, 9.7]
Indication for surgery - no response to PPI	0.7, [-1.46, 2.18]	0.99, [-11.3, 11.2]	0.3, [-1.45, 4.52]	0.4, [-3.3, 8.2]	0.42, [-13, 30]	0.54, [-4.5, 8.5]
Indication for surgery - patient preference	0.66, [-1.4, 2.2]	0.99, [-11.3, 11.4]	0.22, [-1.14, 5]	0.44, [-3.5, 8.1]	0.33, [-11, 32]	0.36, [-3.5, 9.6]

LA grade of oesophagitis	0.94, [-0.12, 0.11]	0.24, [-0.33, 1.3]	0.14, [-0.37, 0.05]	0.96, [-0.44, 0.42]	0.49, [-1, 2.1]	0.06, [-0.94, 0.03]
No hiatus hernia	0.22, [-0.11, 0.51]	0.74, [-1.78, 2.48]	0.42, [-0.8, 0.33]	0.23, [-0.39, 1.6]	0.72, [-3.1, 4.4]	0.31, [-1.7, 0.55]
Hiatus hernia less than 2cm	0.6, [-0.26, 0.45]	0.78, [-2, 2.7]	0.44, [-0.4, 0.88]	0.64, [-1.3, 0.85]	0.83, [-4.6, 3.7]	0.79, [-1, 1.4]
24hr Percentage pH<4	0.17, [-0.03, 0.2]	0.16, [-0.23, 1.34]	0.18, [-0.34, 0.06]	0.09, [-0.05, 0.72]	0.58, [-1, 1.8]	0.14, [-0.76, 0.11]
% Oesophageal peristalsis	**<0.03, [-0.2, -0.007]***	0.27, [-1.23, 0.35]	**<0.002, [0.13, 0.5]***	0.43, [-0.58, 0.25]	**<0.02, [-3.4, -0.2]***	**<0.009, [0.15, 1.1]***
LOS/ OGJ resting pressure	0.46, [-0.2, 0.08]	0.22, [-0.35, 1.47]	0.17, [-0.41, 0.07]	0.72, [0.55, 0.38]	0.17, [-0.53, 2.9]	0.62, [-0.6, 0.39]
LOS nadir pressure	0.62, [-0.1, 0.17]	0.23, [-1.5, 0.36]	**0.04, [0.003, 0.5]***	0.19, [-0.16, 0.8]	**0.04, [-3.7, -0.09]***	0.34, [-0.28, 0.79]

4.3.4 Accuracy of regression versus machine learning models

The accuracy of the model was assessed using Root Mean Squared Error (RMSE) for the training and test datasets (as described above) for the outcome measures of heartburn, dysphagia, and satisfaction (**Figure 2**).



Figures 4.2 Comparison of multivariate analysis models with heartburn, dysphagia, and satisfaction as the primary outcome measure after laparoscopic fundoplication for reflux. Seven different models are shown on the X-axis; the first three are regression analysis models, and last four are machine learning models. RMSE (Root Mean Square Error) is denoted on the Y-axis, which reflects the accuracy of the model, i.e. between the actual score and predicted score.

Model accuracy improved slightly when missing data fields remained empty, rather than imputed by median values for heartburn as the outcome measure. However, model accuracy was better when missing data was imputed for dysphagia score and satisfaction score as outcome measures (**Table 9**). The most accurate model overall for predicting patient outcome after fundoplication was machine learning regression-based LASSO algorithms for heartburn score as the outcome measure (**Table 10**).

Table 4-9 Model accuracy using Root Mean Squared Error (RMSE) with missing observations imputed Using median values. Numbers in bold type with asterix indicate the best model based on the test dataset accuracy.

	Heartburn Score (Range 0 - 10)		Dakkak & Bennett Score (Range 0 - 45)		Satisfaction (Range 0 - 10)	
Model	Train (N=625)	Test (N=269)	Train (N=625)	Test (N=269)	Train (N=625)	Test (N=269)
Mean score						
Regression models						
No predictors	2.57	2.71	10.04	10.16	2.64	3.08
Negative Binomial Stepwise	2.47	2.72	9.75	10.05	2.59	3.10
Negative Binomial All predictors	2.46	**2.69***	9.70	10.04	2.57	**3.07***
ML algorithms						
Decision Tree	2.40	2.84	9.57	10.30	2.52	3.18
Random Forest	2.31	2.75	9.60	**9.95***	0.97	3.12
Support Vector	2.61	2.865	10.05	10.44	2.73	3.34
LASSO	2.48	2.70	9.79	10.04	2.62	3.09

ML, machine learning; LASSO, Least Absolute Shrinkage Support Operator ML model

Table 4-10 Model accuracy using Root Mean Squared Error (RMSE) with missing observations deleted. Numbers in bold type with asterix indicate the best model based on the test dataset accuracy.

	Heartburn Score (Range 0 - 10)		Dakkak & Bennett Score (Range 0 - 45)		Satisfaction (Range 0 - 10)	
Model	Train (N=221)	Test (N=60)	Train (N=221)	Test (N=60)	Train (N=221)	Test (N=60)
Mean score						
Regression models						
No predictors	2.51	2.38	9.41	10.51	2.84	**3.25***
Linear regression Stepwise	2.30	2.46	8.67	10.91	2.60	3.72
Negative Binomial All predictors	2.28	2.39	8.56	11.30	2.56	3.71
ML algorithms						
Decision Tree	2.25	2.385	9.11	**10.40***	2.74	3.48
Random Forest	2.02	2.38	9.02	10.50	2.71	3.35
Support Vector	2.37	2.535	8.81	11.86	2.71	3.86
LASSO	2.37	**2.34***	8.93	10.50	2.70	3.45

ML, machine learning; LASSO, Least Absolute Shrinkage Support Operator ML model

4.4 Discussion

4.4.1 Univariate Analysis

Male patients had a significant improvement and/or resolution of heartburn post-operatively compared to females. This has been reported in other studies where females had a higher risk of both developing recurrent reflux symptoms and reporting higher heartburn scores (Beck et al., 2009, Maret-Ouda et al., 2017). Symptom index (SI) on a 24h pH study was the single most important predictor amongst all examined parameters reported with a pH study. SI had a statistically significant negative correlation with post fundoplication heartburn score. None of the other parameters, including percentage time pH<4 (acid exposure time), predicted heartburn score. The results are consistent with other studies on symptom index (Agrawal and Castell, 2008, Rossetti et al., 2014). A third and final significant predictor for heartburn was the percentage of distal oesophageal peristalsis. Effective oesophageal motility was an independent predictor for a lower heartburn score after surgery. This finding was reflected in a study by Broeders et al (Broeders et al., 2011b).

Post fundoplication dysphagia was more thoroughly evaluated using three different symptom outcome scores: 1) dysphagia to liquids, 2) dysphagia to solids, and 3) the Dakkak dysphagia score. The pattern or severity of pre-operative dysphagia did not affect the selection of GORD patients for fundoplication. However, the presence of ineffective oesophageal motility and/or aperistalsis may have influenced the surgeon's decision to perform a partial versus total fundoplication.

Our study found that severe pre-operative dysphagia to liquids and/or solids increased the risk of post-operative dysphagia to liquids and/or solids as well as a higher Dakkak & Bennett dysphagia score. This finding is supported by some studies (Kapadia et al., 2018, Wilshire et al., 2012, Montenovo et al., 2009, Hasak et al., 2019) but not others (Fumagalli et al., 2008, Sato et al., 2002). The presence of an oesophageal stricture was also found to statistically increase the risk of dysphagia to liquids after fundoplication. The satisfaction score was significantly lower in this small subset of patients. And, once again, females were more likely to complain of dysphagia to liquids and solids after fundoplication.

Hiatus hernia and effective peristalsis were the only two factors that predicted higher satisfaction after fundoplication. Hiatus hernia was reported in 45.4% of patients (26.9% had small hiatus hernias, and 18.5% were between 2 and 5cm in size). Medium-sized hiatus hernias were found to have a strong negative correlation (r = -1.2) with post fundoplication satisfaction scores in multivariate analysis along

with percentage of peristalsis (r = 0.2). A study by Miholic et al. reported higher reflux recurrence rate (22%) for medium sized hiatal hernias compared to smaller or no hiatus hernia (7%, p = 0.005). In multivariate analysis, medium sized hernias had risk ratio of 3.8 (p < 0.001) for symptom recurrence (Miholic et al., 2012).

4.4.2 Regression and Machine Learning models

After a comprehensive scoping review and interrogation of a mature, prospectively managed fundoplication database, the most influential predictor for good heartburn control and a lack of dysphagia after laparoscopic fundoplication was male sex. The percentage of primary peristalsis noted on the pre-operative oesophageal manometry was the second most influential predictor.

Male sex as a positive predictor of outcome after fundoplication was reported previously by our group (Staehelin et al., 2014), using a shorter follow-up interval (1-3 years). It was also reported by a group in the U.K. They found that female patients reported significantly higher DeMeester symptom scores and lower satisfaction than male patients at a median follow-up of 83 months (Robertson et al., 2017). The reason for this finding is unclear. There is no doubt that female patients are more likely to report gas-related symptoms post-fundoplication compared to male patients (Cockbain et al., 2019), without any significant impact on quality of life. However, from this research, one could surmise that female patients may also be more likely to notice minor recurrent symptoms compared to their male counterparts.

Poor oesophageal peristalsis is common in patients with reflux disease and described previously as a significant factor affecting patients with recurrent reflux after fundoplication (Broeders et al., 2011b). Reduced oesophageal peristalsis may lead to poor oesophageal bolus transport and/or inadequate reflux clearance in these patients, leading to higher post-operative heartburn scores and lower patient satisfaction rates.

At five-years post-surgery, an 87% majority reported that they made the correct decision by having laparoscopic fundoplication. This figure corresponds with other high-volume centers where 78 to 87% were satisfied with their decision to undergo surgery (Dallemagne et al., 2006, Morgenthal et al., 2007c). It is interesting to note that 92% of our cohort reported typical symptoms pre-operatively, which may explain our high satisfaction rate at 5 years. In addition, almost two thirds of patients had no hiatus

hernia or a hernia less than 2cm in size, allowing for a uniform patient population with reflux as the primary indication for surgery.

Very little difference was found between the regression and machine learning models for predicting a good outcome after fundoplication. As anticipated, predictive accuracy was better for training data (complete dataset without imputation). However, the best predictive accuracy was found for both heartburn and dysphagia – using machine learning model LASSO and Decision Tree algorithms, respectively. Predictive accuracy for outcome satisfaction score was best when using regression models with no predictors!

Similar results to ours were reported in three recent systematic reviews evaluating the use of machine learning algorithms in cardiac surgery (Penny-Dimri et al., 2022), colorectal surgery (Bektas et al., 2022), and bariatric surgery (Enodien et al., 2023) to predict outcomes. Since 2020, there has been an exponential increase in publications using applied machine learning models. But, despite the potential of machine learning models to refine clinical decision-making, they do not appear to be superior to current statistical methods at the present time and should be used as a research tool only.

There are several limitations to our study. Patients included in our institutional laparoscopic fundoplication database were pre-screened and selected for surgery by experienced upper gastrointestinal surgeons. Very few (15.6%) had atypical symptoms, showing our institutional bias to select patients who want surgical treatment of typical reflux symptoms, thus are more likely to have a successful outcome after anti-reflux surgery. Perhaps a more accurate model would be found if “allcomers” underwent surgery, i.e. if we offered anti-reflux surgery to all patients with pathological oesophageal acid exposure, irrespective of symptoms and motility.

4.5 Conclusion

Male sex was the most accurate predictor of a good outcome after laparoscopic fundoplication. The reason for this finding is not clear. However, in the scenario of an ambivalent case, a female patient undecided between medical therapy and surgical fundoplication, perhaps it is wise to err towards medical therapy. As far as the inclusion of machine learning algorithms in our clinical decision-making process, it is clear machine learning is not yet sufficiently advanced enough to replace clinical acumen for selecting patients who will have a good outcome after fundoplication.

5. Conclusions and final thoughts

5.1 Conclusions

5.1.1 Aim Number 1

To identify all potential pre-operative predictors which may correspond to a successful outcome following a laparoscopic fundoplication based on a narrative review of the literature (manuscripts published between 1995 and 2000).

Several potential pre-operative predictors were discovered, some of which were not evaluated thoroughly in the past. Table 4-1 summarises the results from the first chapter of this thesis:

Preoperative factors	Predictive strength for a good outcome
1. Age 2. Sex 3. Body mass index 4. Typical vs atypical symptoms 5. Response to anti-reflux medications 6. Endoscopy 7. Reflux test/ pH studies 8. Manometry 9. Barium oesophagogram	None Male gender* BMI <30 kg/m²* Typical symptoms*** Good responder*** None Positive pH study None None
Legend: strength of predictor: *, some evidence; ***, strong evidence	

5.1.2 Aim Number 2

To determine which of the potential predictors identified in Aim #1 were most influential in the occurrence of a successful outcome after fundoplication with a systematic review.

The systematic review identified male sex, typical symptoms, a good response to anti-reflux medication, and an abnormal pre-operative pH study as the best predictors of a good outcome after laparoscopic fundoplication. Age, weight, grade of oesophagitis, oesophageal peristaltic function, and reflux patterns

did not affect patient outcome nor satisfaction. By contrast, patients with depression, isolated atypical symptoms, delayed gastric emptying, and long segment Barrett's oesophagus were found to report less favourable surgical outcomes. As well, elderly patients with reflux disease, patients with equivocal or negative pH studies, and pre-operative dysphagia with a hypertensive lower oesophageal sphincter were identified as pre-operative predictors requiring careful consideration. These factors should prompt caution and a need for further work-up prior to surgical intervention.

5.1.3 Aim Number 3

To use the best predictors of a successful outcome after fundoplication identified in Aim #2 to interrogate the Flinders Medical Centre's institutional large, prospectively-maintained database. For this Aim, a univariate analysis was performed first, followed by regression and machine learning analysis to identify, and validate preoperative variables which are most influential in predicting patient outcomes at 5 years after laparoscopic fundoplication.

The most influential predictor for good heartburn control and a lack of dysphagia after laparoscopic fundoplication was male sex. The reason for this finding is not clear. However, in the scenario of an ambivalent case, a female patient undecided between medical therapy and surgical fundoplication, perhaps it is wise to err towards medical therapy. The percentage of primary peristalsis noted on the pre-operative oesophageal manometry was the second most influential predictor.

As far as the inclusion of machine learning algorithms in our clinical decision-making process, it is clear that machine learning is not yet sufficiently advanced enough to replace clinical acumen for selecting patients who will have a good outcome after fundoplication.

5.2 Final thoughts

This Master of Surgery thesis has confirmed that the most influential predictor of a successful outcome after laparoscopic fundoplication is sex. We found a lesser improvement or resolution of heartburn and a higher degree of dysphagia in females compared to males after fundoplication. This has been described before and this thesis lends to the literature base to support this result as a true predictor. That said, this was only a modest difference, and it is not strong enough to dissuade all females from a laparoscopic fundoplication. Our results simply show that if the decision for fundoplication is equivocal, surgeons should err on the side of caution before proceeding to surgery. It is also important to set realistic expectations with the patient on likely outcomes after fundoplication, especially regarding post-surgery side-effects such as bloating, increased flatulence, inability to belch, and dysphagia. Although one expects these side-effects to dissipate over time, they can contribute to decreased satisfaction levels in the short term.

Whilst this body of work found a couple of robust predictors of outcome after fundoplication, there is insufficient data and support for an algorithmic approach for choosing the right patient for an operation. Further work is needed!

This Master of Surgery thesis used artificial intelligence (machine learning; ML) to enhance the statistical analysis of the potential predictors, using a mature prospectively maintained fundoplication database. Though the use of ML analysis provided excellent accuracy, their performance was similar to regression analysis. It is fairly clear that ML algorithms will not replace surgical acumen at this point in time!

There were several limitations in this Thesis. The definition of a successful fundoplication is not entirely clear in the literature. Whilst conducting this body of work, nearly 20 different subjective outcome scores were found, which increased the complexity of the narrative review, and subsequent regression and ML analysis. Consensus on best outcome measures would be useful and will standardise future systematic reviews and meta-analyses. This was a limitation in Chapter 3 as studies were too heterogeneous to allow for a meaningful meta-analysis. We recommend the gastro-oesophageal reflux disease (GORD) health-related quality of life or GORD-hr-QOL, heartburn score, dysphagia score and satisfaction score. Whilst failures based on low subjective scores are investigated further through objective investigations including endoscopy, pH study, or manometry, the greatest challenge is to

obtain objective measures as patients are not always keen to undergo repeat endoscopy and/or 24hr pH/manometry following surgery.

In addition, for Chapter 4, patients included in our institutional laparoscopic fundoplication database were pre-screened and selected for surgery by experienced upper gastrointestinal surgeons. Very few (15.6%) had atypical symptoms, showing our institutional bias to select patients who want surgical treatment of typical reflux symptoms, thus are more likely to have a successful outcome after anti-reflux surgery. Perhaps a more accurate model would have been found if "all-comers" underwent surgery, i.e. if we offered anti-reflux surgery to all patients with pathological oesophageal acid exposure, irrespective of symptoms and motility.

Nevertheless, our institutional database is mature, and we only included patients with a follow-up of 5 years post-laparoscopic fundoplication. We found that 87% of patients reported that they made the correct decision by having laparoscopic fundoplication. It is with this final statistic that we conclude that clinical acumen is the best tool for selecting patients who will have a favourable outcome after laparoscopic fundoplication.

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