

# Gas and Bloat in Female Patients after Antireflux Procedures: Analysis of 934 Cases

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- BACKGROUND:** Antireflux procedures (ARPs) are effective treatments for GERD. However, variation in objective and patient-reported outcomes persists. Limited evidence and anecdotal experience suggest that patient sex may play a role. The objective of this study was to compare outcomes after ARPs between male and female patients.
- STUDY DESIGN:** We performed a retrospective review of a prospectively maintained database at a single institution. All patients who underwent an ARP for GERD were included. Demographic, clinical, and patient-reported outcomes data (GERD health-related quality of life [HRQL] and reflux symptom index), and radiographic hernia recurrence were collected and stratified by sex. Univariable and multivariable logistic and mixed-effects linear regression were used to control for confounding effects.
- RESULTS:** Between 2009 and 2022, 934 patients (291 men and 643 women) underwent an ARP. Reflux symptom index, GERD-HRQL, and gas and bloat scores improved uniformly for both sexes, though female patients were more likely to have higher gas and bloat scores 1 year postprocedure (mean  $\pm$  SD  $1.7 \pm 1.4$  vs  $1.4 \pm 1.3$ ,  $p = 0.03$ ) and higher GERD-HRQL scores 2 years postprocedure ( $6.3 \pm 8.1$  vs  $4.7 \pm 6.8$ ,  $p = 0.04$ ). Higher gas and bloat scores in women persisted on regression controlling for confounders. Hernia recurrence rate was low (85 patients, 9%) and was similar for both sexes. A final intraprocedural distensibility index  $3 \text{ mm}^2/\text{mmHg}$  or more was significantly associated with a 7 times higher rate of recurrence (95% CI 1.62 to 31.22,  $p = 0.01$ ).
- CONCLUSIONS:** Although patients of either sex experience symptom improvement and low rate of recurrence after ARPs, women are more likely to endorse gas and bloat compared with men. Final distensibility index  $3 \text{ mm}^2/\text{mmHg}$  or more carries a high risk of recurrence. These results may augment how physicians prognosticate during consultation and tailor their treatment in patients with GERD. (J Am Coll Surg 2024;239:18–29. © 2024 by the American College of Surgeons. Published by Wolters Kluwer Health, Inc. All rights reserved.)

GERD affects ~10% to 15% of US patients on a weekly basis, leading to decreased health-related quality of life (HRQL).<sup>1,2</sup> Antireflux procedures (ARPs), ranging from endoscopic to surgical, are proven treatments for GERD with good outcomes.<sup>3</sup> However, despite improvement in technique over time and relative standardization of

technical approaches,<sup>4</sup> variation in postprocedural outcomes persists.

Gender- and sex-based differences are thought to play a role in this variation, beginning before undergoing any ARP. For example, Lin and colleagues<sup>5</sup> found that women referred for GERD treatment experience significantly

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**Abbreviations and Acronyms**

ARP	=	antireflux procedure
DI	=	distensibility index
FLIP	=	functional lumen imaging probe
HH	=	hiatal hernia
HRQL	=	health-related quality of life
LES	=	lower esophageal sphincter
PEH	=	paraesophageal hernia
PPI	=	proton pump inhibitor
RSI	=	reflux symptom index

worse heartburn, regurgitation, belching, and nocturnal GERD symptoms than men, and a study of Australian patients with GERD by Chen and colleagues<sup>6</sup> found that women in the community were more likely to report heartburn than men and had higher symptom severity. With regard to postprocedure outcomes, Beck and colleagues<sup>7</sup> reviewed the outcomes of 733 patients who underwent laparoscopic fundoplasty for GERD and found that female patients had higher heartburn and dysphagia scores compared with men and were less satisfied postoperatively. Oelschlager and colleagues<sup>8</sup> also reviewed 441 patients who underwent laparoscopic antireflux surgery and found that being male was a predictor for symptom resolution.

Although the latter 2 studies were performed with good rigor, they did not use standardized HRQL scores in their data collection and reporting. Based on our own anecdotal experience, we have long suspected that the impact of proton pump inhibitors (PPIs) on patients' lives and the effects of gas and bloat symptoms would vary significantly by patient sex—both elements missing in the literature. Third, to date, no studies have investigated sex-based differences in intraprocedural functional lumen imaging probe (FLIP) parameters. Therefore, we sought to investigate how these specific outcomes vary by sex at our own institution.

**METHODS****Data source**

We performed a retrospective review of an IRB-approved prospectively maintained quality database at a single high-volume institution (more than 150 foregut procedures per year, NorthShore University HealthSystem, Evanston, IL) in June 2023. All patients who underwent a surgical or endoscopic ARP for GERD were included. Surgical procedures included fundoplication (complete or partial) and magnetic sphincter augmentation, whereas endoscopic procedures were made up of antireflux mucosectomy. Patients who underwent an ARP at the time of another primary procedure (ie myotomy for achalasia) were excluded. Patient demographics, perioperative clinical data, including 30-day outcomes, manometric data, pH study parameters, hiatal hernia (HH) type, and procedure type were collected. Patient sex was determined by abstraction from the electronic medical record demographic file. Radiographic hernia recurrence was identified via chart review as part of routine database upkeep and therefore included both symptomatic patients undergoing workup with CT studies, upper gastrointestinal studies, and esophagrams as indicated, and asymptomatic patients with incidentally discovered hernia recurrence while undergoing radiographic studies for other indications.

**Objective outcomes**

Periprocedural objective outcomes included any intraprocedural complication, pain at discharge, median time to narcotic pain medication stoppage, median time to return to activities of daily living, and standard 30-day outcomes (complication, ED visit, and hospital readmission). Rates of PPI cessation postprocedure and radiographic hernia recurrence were also collected. Intraoperative FLIP assessment of the lower esophageal sphincter (LES) was collected where available and included the minimum diameter (mm), pressure (mmHg), cross-sectional area (mm<sup>2</sup>), and distensibility index (DI, mm<sup>2</sup>/mmHg). We have published our research protocol for FLIP measurements previously.<sup>9</sup> Specifically, the “final” FLIP measurement performed at the conclusion of the procedure were included for analysis here.

**Patient-reported outcomes**

Reflux symptom index (RSI), GERD-HRQL, and dysphagia scores were collected at 8 different time points: preprocedure, 3 weeks, 6 months, 1 year, 2 years, 5 years, 7 years, and 10 years postprocedure. The RSI is a validated 9-item questionnaire developed to assess laryngopharyngeal reflux and is a surrogate for atypical GERD symptoms.<sup>10</sup> Scores from each item are added to produce a final score ranging from 0 (no

<p>GERD-HRQL Item#10: If you take anti-reflux medication, does this affect your daily life?</p> <p>RSI Item #1: Within the last month, how did hoarseness or a problem with your voice affect you?</p> <p>RSI Item #7: Within the last month, how did troublesome or annoying cough affect you?</p>
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**Figure 1.** Individual items from the GERD health-related quality of life (GERD-HRQL) and reflux symptom index (RSI) scores selected for analysis by sex.

symptoms) to 45 (severe symptoms). The GERD-HRQL questionnaire was developed to assess typical GERD symptoms.<sup>11</sup> The questionnaire consists of 11 items from which a final score is calculated ranging from 0 (asymptomatic) to 50 (severe GERD symptoms). Two items from the RSI and 1 from the GERD-HRQL questionnaire whose responses we hypothesized would vary by sex were analyzed and reported separately (Fig. 1). These specific items were selected based on our anecdotal experience that female patients more frequently expressed concern regarding use of antireflux medication, voice change or hoarseness, and cough symptoms. We analyzed and reported responses to the GERD-HRQL item “Do you have gassy or bloating feelings?” separately as the gas and bloat score. Scores ranged from 0 to 5, with a score greater than 1 considered symptomatic. The dysphagia score is the response to a question regarding postprocedure dysphagia ranging from 1 (no dysphagia) to 5 (severe dysphagia). A score greater than 1 was considered symptomatic. Finally, percent symptom resolution was also included in analysis. This patient-reported measure is collected at each postprocedure visit wherein the patient is asked to rate to what percentage each of their symptoms have improved relative to their preprocedure baseline. Zero percent signifies no improvement and 100% signifies complete symptom resolution or absence of symptoms.

### Analysis

Summary statistics were used to describe perioperative characteristics of the entire cohort and characteristics stratified by sex. Differences between sexes were evaluated using 2-sample *t*-test, Wilcoxon rank sum, chi-square, or Fisher's exact tests, where appropriate. Wilcoxon rank-sum tests and linear regression were used to evaluate postprocedure patient-reported outcomes at all time points. Items with significant differences in responses between sexes were then included in multivariable models to identify predictors. Linear mixed models were used to identify predictors of gas and bloat scores and logistic regression was used to identify predictors of radiographic hernia recurrence. Finally, subgroup analyses were performed using all patients with intraprocedural FLIP data for both linear mixed and logistic regression models to control for final DI as a possible confounder. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

### RESULTS

Between 2009 and 2022, 291 male and 643 female patients underwent an ARP at the study institution. Follow-up occurred between 2009 and the time of the retrospective review in 2023. Median follow-up was 5 months (interquartile range 1 to 24) and did not differ between male patients (4, interquartile range 1 to 18) and female patients (6, interquartile range 1 to 27),  $p = 0.0948$ . Female patients were more likely to be older, to have a higher BMI, and to have never smoked than male patients (Table 1). Female patients were more likely to have dysphagia, epigastric chest pain, and Barrett's esophagus on presentation and were more likely to have a paraesophageal hernia (PEH) than male patients. Partial (Toupet and Dor) fundoplication was the most common procedure performed for both sexes (430, 46%), followed by Nissen fundoplication (389, 42%), antireflux mucosectomy (59, 6%), and magnetic sphincter augmentation (56, 6%; Table 2). Procedure type did not differ significantly between sexes. Final intraprocedural FLIP parameters, perioperative outcomes, and 30-day outcomes were also similar, and both groups had similar percent symptom resolution for all symptoms except for epigastric chest pain, which was more likely to persist in female patients (female patients 79% vs 21% male patients). The overall rate of radiographic recurrence was 9% (85 patients). More female patients recurred than male patients (67 vs 18, respectively,  $p = 0.04$ ). Age was not correlated with recurrence or patient-reported outcome scores. Response rates to patient-reported outcome questionnaires varied at different time points and generally decreased throughout the study, ranging from 54% preprocedure to 4% at 10 years postprocedure (Table 3). Preprocedure RSI, GERD-HRQL, and dysphagia scores were similar among sexes when controlling for hernia type, operation type, recurrence, and preprocedure diagnosis of Barrett's esophagus. However, female patients were more likely to endorse significant gas and bloating symptoms despite controlling for these confounders. Patients' typical and atypical symptoms, including gas and bloat, uniformly improved from pre- to postprocedure, with most change occurring within the first 6 months (Fig. 2). Dysphagia scores worsened for all patients at the 3-week mark but then returned to baseline thereafter.

**Table 1.** Preprocedure Patient Characteristics by Sex

Variable	All	Male sex	Female sex	p Value
Total patients, n (%)	934 (100)	291 (31)	643 (69)	
Age, y, mean $\pm$ SD	65 $\pm$ 3	63 $\pm$ 14	66 $\pm$ 13	0.01*
BMI, kg/m <sup>2</sup> , mean $\pm$ SD	29.0 $\pm$ 5.1	28.1 $\pm$ 4.6	29.5 $\pm$ 5.3	<0.01*
Obese, n (%)	356 (40)	88 (30)	268 (41)	<0.01*
Smoking status, n (%)				<0.01*
Never	545 (58)	148 (50)	397 (61)	
Former	367 (40)	132 (45)	235 (36)	
Current	22 (2)	11 (3)	11 (1)	
Diabetes, n (%)	79 (9)	20 (6)	59 (9)	0.24
Preprocedure symptoms, n (%)				
Heartburn	692 (74)	217 (74)	475 (73)	0.82
Dysphagia	373 (40)	94 (32)	279 (43)	<0.01*
Regurgitation	594 (64)	177 (60)	417 (64)	0.24
Cough	290 (31)	97 (33)	193 (30)	0.31
Epigastric chest pain	316 (34)	65 (22)	251 (39)	<0.01*
Barrett's esophagus, n (%)	64 (7)	35 (12)	29 (4)	<0.01*
American Society of Anesthesiologists class 3 or 4, n (%)	369 (40)	112 (38)	257 (39)	0.67
Esophageal motility, n (%)				0.39
Normal†	589 (63)	180 (61)	409 (63)	
Ineffective	185 (20)	65 (22)	120 (18)	
Unknown/no manometry	160 (17)	46 (15)	114 (17)	
Preprocedure DeMeester score, median (interquartile range), N = 316	30.9 (19.3–51.1)	34.1 (19.5–58.5)	29.2 (18.5–44.9)	0.06
DeMeester >14.7, n (%)	266 (84)	106 (36)	160 (24)	0.58
Hernia type, n (%)				<0.01*
None	120 (13)	49 (16)	71 (11)	
Hiatal hernia/type I	260 (28)	112 (38)	148 (23)	
Paraesophageal hernia/type II–IV	554 (60)	130 (44)	424 (65)	

\*Statistically significant difference between sexes,  $p < 0.05$ .

†80% or more normal swallows on manometry.

Responses to individual items from the GERD-HRQL and RSI scores varied throughout the follow-up period (Table 4). In particular, responses to GERD-HRQL item no. 10, which assesses patients' perceived impact of taking daily antireflux medication, were significantly worse among female patients compared with male patients even when controlling for hernia type, operation type, recurrence, and preprocedure diagnosis of Barrett's esophagus. In a linear mixed model for responses to this GERD-HRQL item, female patients persistently scored higher (worse) than male patients on both univariate and multivariate analysis ( $0.20 \pm 0.07$  points,  $p < 0.01$ , Table 5). This persisted when controlling for DI on subgroup analysis of all patients with final intraprocedural FLIP data. Presence of a PEH instead of an HH was predictive of

consistently lower (better) scores on this item of the GERD-HRQL questionnaire.

Female patients were also more likely to have higher (worse) gas and bloat scores than male patients, even when controlling for hernia type, fundoplication type, postoperative PPI use, age, and hernia recurrence ( $0.34 \pm 0.09$  points higher,  $p < 0.01$ , Table 6). This was also found on subgroup analysis controlling for DI ( $0.52 \pm 0.15$  points higher,  $p < 0.01$ ). Increasing age was associated with less gas and bloat on univariate, multivariate, and subgroup analyses for both sexes. The presence of a PEH instead of an HH was predictive of less gas and bloat symptoms for patients of either sex ( $0.30 \pm 0.18$  points less,  $p = 0.02$ ), but this did not persist in subgroup analysis controlling for final DI. The type of fundoplication performed was not predictive of gas and bloat scores.

**Table 2.** Intra- and Postprocedure Patient Characteristics

Variable	All	Male sex	Female sex	p Value
Intraprocedure characteristic				
Operation type, n (%)				
Nissen	389 (42)	109 (37)	280 (43)	0.08
Toupet/Dor	430 (46)	138 (47)	292 (45)	0.57
Magnetic sphincter augmentation	56 (6)	24 (8)	32 (4)	0.05
Antireflux mucosectomy	59 (6)	20 (6)	39 (6)	0.64
Final intraprocedure functional luminal imaging probe measurement, mean $\pm$ SD, N = 336				
Minimum diameter, mm	11.3 $\pm$ 2.4	11.5 $\pm$ 2.5	11.2 $\pm$ 2.3	0.26
Pressure, mmHg	34 $\pm$ 9	34 $\pm$ 9	34 $\pm$ 9	0.52
Cross-sectional area, mm <sup>2</sup>	104 $\pm$ 42	107 $\pm$ 46	102 $\pm$ 40	0.45
Distensibility index, mm <sup>2</sup> /mmHg	3.2 $\pm$ 1.4	3.4 $\pm$ 1.5	3.1 $\pm$ 1.3	0.13
Operating room time, min, mean $\pm$ SD	122 $\pm$ 48	123 $\pm$ 52	121 $\pm$ 46	0.79
Estimated blood loss, mL, median (IQR)	10 (5–25)	10 (5–25)	10 (5–25)	0.61
Redo procedure, n (%)	75 (8)	26 (8)	49 (7)	0.5
Intraprocedural complication, n (%)	32 (3)	6 (2)	26 (4)	0.12
Postprocedure characteristic				
Return to activities of daily living, d, median (IQR), N = 477	5 (2–7)	4 (2–7)	5 (2–7)	0.01*
30-d outcomes, n (%)				
Mortality	3 (<1)	2 (0)	1 (0)	0.18
Complication	81 (9)	22 (7)	59 (9)	0.42
Emergency department visit	100 (11)	31 (10)	69 (10)	0.97
Readmission	61 (7)	21 (7)	40 (6)	0.57
Postoperative of proton pump inhibitor at 1 y, n (%), N = 702	564 (80)	173 (59)	391 (60)	0.83
Symptom resolution, n (%)				
Heartburn, N = 496	425 (86)	128 (43)	297 (46)	0.27
Dysphagia, N = 327	232 (71)	54 (18)	178 (27)	0.33
Regurgitation, N = 439	373 (85)	100 (34)	273 (42)	0.18
Cough, N = 210	145 (69)	51 (17)	94 (14)	0.38
Epigastric chest pain, N = 232	180 (78)	38 (13)	142 (22)	0.24
Recurrence, n (%)	85 (9)	18 (6)	67 (10)	0.04*
Postoperative DeMeester score, median (IQR), N = 102	7.1 (3.4–16.3)	5.3 (3.0–14.1)	8.8 (3.7–17.0)	0.25
DeMeester >14.7, n (%)	30 (29)	8 (2)	22 (3)	0.24

\*Statistically significant difference between sexes,  $p < 0.05$ . IQR, interquartile range.

On logistic regression for recurrence, female patients were 1.7 times more likely to recur compared with male patients on univariate analysis (95% CI 1.01 to 2.96,  $p = 0.04$ ). However, this did not persist in multivariate analysis controlling for BMI, smoking status, hernia type, procedure type, presence of intraprocedural complication, and whether or not the procedure was a redo foregut procedure (odds ratio [95% CI] 1.29 [0.74 to 2.24],  $p = 0.37$ ). Recurrence was 6.6 times higher for patients

with PEH than those with HH in the model (95% CI 2.79 to 15.89,  $p < 0.01$ ). However, on subgroup analysis controlling for DI, this characteristic was no longer a significant predictor of recurrence. The type of ARP performed was not predictive of recurrence except when comparing Nissen fundoplication with Toupet fundoplication: Nissen fundoplication was predictive of recurrence on both univariate and multivariate analyses. However, this did not persist on subgroup analysis when controlling for

**Table 3.** Patient-Reported Outcomes over Time

Variable	All, mean $\pm$ SD, N = 501	Male sex, mean $\pm$ SD, N = 157	Female sex, mean $\pm$ SD, N = 344	Raw p value*	Adjusted p value†
Preprocedure					
RSI	17.2 $\pm$ 10.8	16.9 $\pm$ 10.4	17.4 $\pm$ 11.0	0.77	0.15
GERD-HRQL	15.1 $\pm$ 10.8	14.5 $\pm$ 10.4	15.4 $\pm$ 11.0	0.41	0.06
Gas and bloat score	2.1 $\pm$ 1.5	1.8 $\pm$ 1.5	2.3 $\pm$ 1.5	>0.01‡	>0.01‡
Dysphagia score	1.3 $\pm$ 0.7	1.2 $\pm$ 0.6	1.3 $\pm$ 0.7	0.02‡	0.09
3 wk postprocedure					
	N = 325	N = 104	N = 221		
RSI	11.2 $\pm$ 9.1	9.6 $\pm$ 8.0	12.0 $\pm$ 9.5	0.06	0.01‡
GERD-HRQL	6.4 $\pm$ 7.0	5.5 $\pm$ 5.7	6.9 $\pm$ 7.5	0.36	0.05
Gas and bloat score	1.6 $\pm$ 1.4	1.4 $\pm$ 1.5	1.7 $\pm$ 1.4	0.04‡	0.04‡
Dysphagia score	2.1 $\pm$ 0.9	2.0 $\pm$ 0.9	2.1 $\pm$ 0.9	0.09	0.02‡
6 mo postprocedure					
	N = 201	N = 66	N = 135		
RSI	9.0 $\pm$ 8.1	8.2 $\pm$ 6.9	9.4 $\pm$ 8.6	0.68	0.15
GERD-HRQL	5.3 $\pm$ 6.4	5.0 $\pm$ 6.4	5.5 $\pm$ 6.4	0.76	0.39
Gas and bloat score	1.7 $\pm$ 1.4	1.6 $\pm$ 1.3	1.7 $\pm$ 1.4	0.57	0.46
Dysphagia score	1.2 $\pm$ 0.5	1.2 $\pm$ 0.6	1.2 $\pm$ 0.5	0.48	0.59
1 y postprocedure					
	N = 318	N = 108	N = 210		
RSI	8.6 $\pm$ 8.5	9.2 $\pm$ 8.3	8.3 $\pm$ 8.5	0.27	0.82
GERD-HRQL	4.8 $\pm$ 6.2	4.2 $\pm$ 5.9	5.1 $\pm$ 6.3	0.06	0.09
Gas and bloat score	1.6 $\pm$ 1.4	1.4 $\pm$ 1.3	1.7 $\pm$ 1.4	0.03‡	0.03‡
Dysphagia score	1.2 $\pm$ 0.5	1.2 $\pm$ 0.6	1.2 $\pm$ 0.4	0.34	0.76
2 y postprocedure					
	N = 288	N = 88	N = 200		
RSI	10.0 $\pm$ 9.8	9.5 $\pm$ 9.7	10.2 $\pm$ 9.8	0.62	0.32
GERD-HRQL	5.8 $\pm$ 7.8	4.7 $\pm$ 6.8	6.3 $\pm$ 8.1	0.15	0.04‡
Gas and bloat score	1.7 $\pm$ 1.5	1.6 $\pm$ 1.5	1.8 $\pm$ 1.5	0.47	0.33
Dysphagia score	1.2 $\pm$ 0.5	1.1 $\pm$ 0.5	1.2 $\pm$ 0.5	0.37	0.59
5 y postprocedure					
	N = 139	N = 45	N = 94		
RSI	9.3 $\pm$ 9.8	8.9 $\pm$ 10.7	9.5 $\pm$ 9.4	0.37	0.50
GERD-HRQL	6.1 $\pm$ 8.1	4.9 $\pm$ 8.2	6.7 $\pm$ 8.0	0.20	0.18
Gas and bloat score	1.6 $\pm$ 1.4	1.4 $\pm$ 1.4	1.7 $\pm$ 1.4	0.25	0.20
Dysphagia score	1.2 $\pm$ 0.6	1.2 $\pm$ 0.7	1.2 $\pm$ 0.6	0.57	0.53
7 y postprocedure					
	N = 90	N = 30	N = 60		
RSI	9.0 $\pm$ 8.4	10.4 $\pm$ 9.4	8.4 $\pm$ 7.9	0.33	0.24
GERD-HRQL	5.1 $\pm$ 6.1	4.0 $\pm$ 4.5	5.6 $\pm$ 6.7	0.47	0.32
Gas and bloat score	1.5 $\pm$ 1.3	1.5 $\pm$ 1.3	1.6 $\pm$ 1.3	0.79	0.81
Dysphagia score	1.1 $\pm$ 0.5	1.1 $\pm$ 0.3	1.1 $\pm$ 0.6	0.95	0.59
10 y postprocedure					
	N = 34	N = 14	N = 20		
RSI	6.7 $\pm$ 7.5	6.6 $\pm$ 7.0	6.7 $\pm$ 8.0	0.87	—
GERD-HRQL	4.7 $\pm$ 5.4	3.6 $\pm$ 4.9	5.5 $\pm$ 5.7	0.26	—
Gas and bloat score	1.3 $\pm$ 1.2	1.2 $\pm$ 1.1	1.5 $\pm$ 1.3	0.60	—
Dysphagia score	1.2 $\pm$ 0.6	1.4 $\pm$ 0.7	1.2 $\pm$ 0.5	0.35	—

\*Wilcoxon rank-sum.

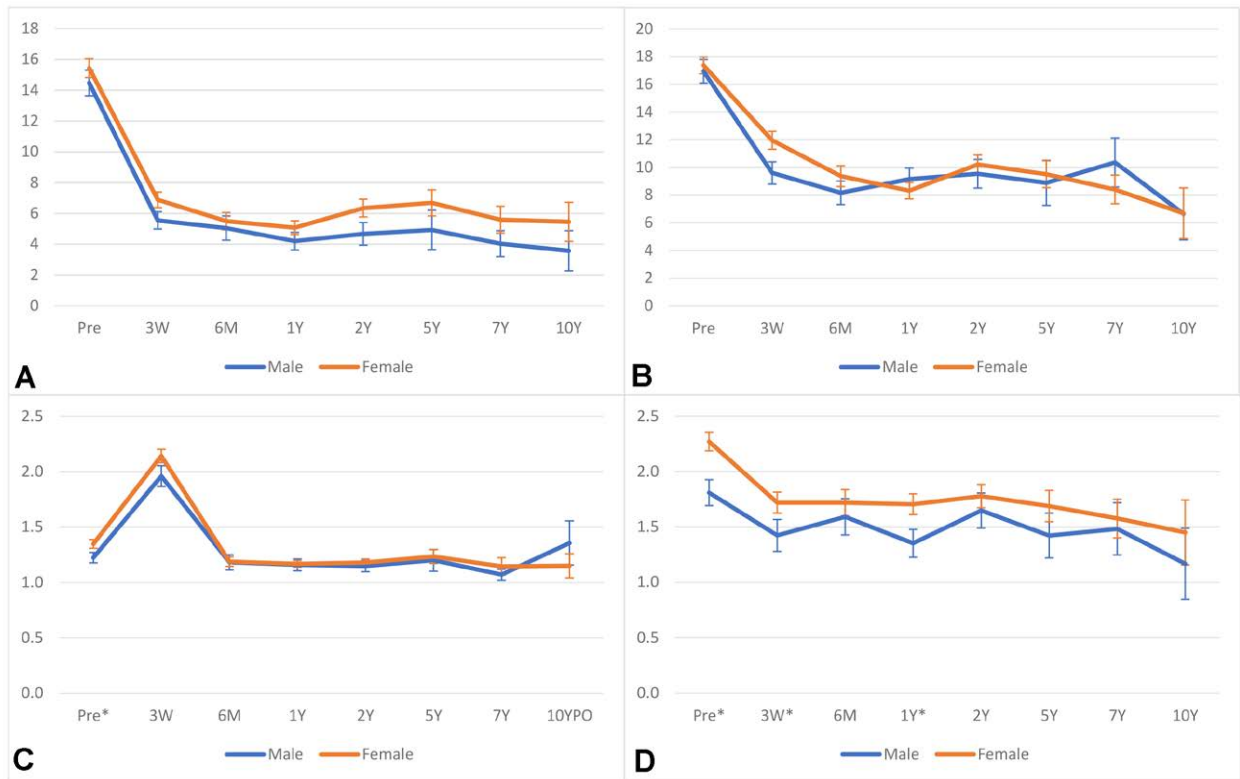
†Linear regression controlling for hernia type, operation type, recurrence, and preprocedure diagnosis of Barrett's esophagus.

‡Statistically significant difference between sexes,  $p < 0.05$ .

GERD-HRQL, GERD health-related quality of life; RSI, reflux symptom index.

final intraoperative DI (odds ratio [95% CI] 0.24 [0.02 to 3.51],  $p = 0.30$ ). Of the patients with intraprocedural FLIP data, those with a DI of 3.0 mm<sup>2</sup>/mmHg or higher

were 7 times more likely to have a recurrence compared with those with a lower DI, regardless of sex, hernia type, or procedure performed (Table 7).



**Figure 2.** Patient-reported outcome scores over time. (A) GERD-HRQL score. (B) RSI score. (C) Dysphagia score. (D) Gas and bloat score. \*Statistically significant difference between sexes,  $p < 0.05$ . GERD-HRQL, GERD health-related quality of life; M, months postprocedure; Pre, preprocedure; RSI, reflux symptom index; W, weeks postprocedure; Y, years postprocedure.

## DISCUSSION

In this single-institution study of 934 prospectively followed patients with GERD who underwent ARPs, we found significant variation in patient-reported outcomes by sex. Although all patients' typical and atypical GERD symptoms improved after their procedure, female patients were more likely to report that taking antireflux medication affects their lives than male patients regardless of confounding factors, such as hernia type, procedure type, radiographic recurrence, and intraoperative FLIP metrics. Female patients were also more likely to experience higher gas and bloat scores than male patients as far out as 1 year postprocedure, regardless of hernia type, type of repair, hernia recurrence, age, and intraoperative final LES distensibility. This did not persist past 1 year. However, when controlling for confounding factors, frequency of recurrence between male patients and female patients was similar. We also found that a complete (Nissen) fundoplication was predictive of recurrence, although this was not sustained on subgroup analysis when controlling for intraoperative final DI. Finally, we found that a DI

of 3 or greater was associated with a 7 times higher rate of recurrence, regardless of patient sex, hernia type, or procedure performed. These findings have implications for clinicians in the preprocedural and intraprocedural spaces.

For clinicians helping patients navigate the decision to pursue an ARP, these findings may change the conversation about postprocedural outcomes, or at the very least encourage a re-evaluation of clinicians' usual "spiel" when discussing what to expect after an ARP. Female patients in our study notably had worse preoperative gas and bloat scores compared with male patients, which may have biased our study toward worse postoperative gas and bloat scores as well. However, we included gas and bloat scores at the preprocedure time point in the linear mixed model to control for this effect—and still detected a statistically significant increase in risk of gas and bloat scores for female patients relative to male patients. That female patients who continue to take or return to antacids postprocedure report that these medications impact their lives more frequently than male patients is not surprising, given the side effects of chronic PPI use that have only recently come to light.

**Table 4.** Individual Items from GERD-Health-Related Quality of Life and Reflux Symptom Index Scores over Time

Variable	All, mean $\pm$ SD	Male, mean $\pm$ SD	Female, mean $\pm$ SD	Raw p value*	Adjusted p value†
Preoperative	N = 473	N = 150	N = 323		
GERD-HRQL item no. 10	1.0 $\pm$ 1.5	0.9 $\pm$ 1.4	1.1 $\pm$ 1.5	0.36	0.05
RSI item no. 1	1.5 $\pm$ 1.7	1.5 $\pm$ 1.7	1.6 $\pm$ 1.7	0.57	0.28
RSI item no. 7	1.7 $\pm$ 1.9	1.7 $\pm$ 1.8	1.6 $\pm$ 1.9	0.53	0.53
3 wk	N = 318	N = 102	N = 216		
GERD-HRQL item no. 10	0.4 $\pm$ 0.9	0.3 $\pm$ 0.7	0.4 $\pm$ 1.0	0.78	0.46
RSI item no. 1	1.0 $\pm$ 1.4	0.9 $\pm$ 1.3	1.0 $\pm$ 1.4	0.97	0.54
RSI item no. 7	1.0 $\pm$ 1.5	0.7 $\pm$ 1.2	1.1 $\pm$ 1.6	0.06	0.02‡
6 mo	N = 197	N = 66	N = 131		
GERD-HRQL item no. 10	0.3 $\pm$ 0.8	0.2 $\pm$ 0.6	0.3 $\pm$ 0.9	0.51	0.37
RSI item no. 1	0.9 $\pm$ 1.4	0.7 $\pm$ 1.2	1.0 $\pm$ 1.4	0.18	0.14
RSI item no. 7	0.9 $\pm$ 1.3	0.6 $\pm$ 1.1	1.0 $\pm$ 1.4	0.16	0.11
1 y	N=317	N=107	N=210		
GERD-HRQL item no. 10	0.3 $\pm$ 0.8	0.2 $\pm$ 0.7	0.3 $\pm$ 0.9	0.16	0.27
RSI item no. 1	0.8 $\pm$ 1.3	0.9 $\pm$ 1.3	0.8 $\pm$ 1.3	0.59	0.87
RSI item no. 7	0.8 $\pm$ 1.4	0.9 $\pm$ 1.5	0.7 $\pm$ 1.3	0.83	0.64
2 y	N = 288	N = 88	N = 200		
GERD-HRQL item no.10	0.5 $\pm$ 1.1	0.3 $\pm$ 0.9	0.6 $\pm$ 1.1	0.03‡	0.15
RSI item no. 1	0.9 $\pm$ 1.3	1.0 $\pm$ 1.3	0.9 $\pm$ 1.3	0.73	0.81
RSI item no. 7	1.0 $\pm$ 1.5	1.0 $\pm$ 1.5	0.9 $\pm$ 1.5	0.34	0.61
5 y	N = 141	N = 45	N = 96		
GERD-HRQL item no.10	0.4 $\pm$ 0.9	0.4 $\pm$ 1.0	0.4 $\pm$ 0.9	0.80	0.80
RSI item no. 1	1.0 $\pm$ 1.5	0.9 $\pm$ 1.5	1.1 $\pm$ 1.5	0.59	0.80
RSI item no. 7	0.9 $\pm$ 1.4	0.9 $\pm$ 1.4	1.0 $\pm$ 1.4	0.60	0.92
7 y	N = 90	N = 29	N = 61		
GERD-HRQL item no. 10	0.3 $\pm$ 0.9	0.1 $\pm$ 0.4	0.5 $\pm$ 1.1	0.03‡	0.02‡
RSI item no. 1	1.0 $\pm$ 1.5	1.2 $\pm$ 1.7	0.9 $\pm$ 1.4	0.43	0.31
RSI item no. 7	0.8 $\pm$ 1.3	1.0 $\pm$ 1.6	0.7 $\pm$ 1.2	0.32	0.18
10 y	N = 34	N = 14	N = 20		
GERD-HRQL item no. 10	0.4 $\pm$ 0.9	0.4 $\pm$ 1.1	0.3 $\pm$ 0.7	0.95	—
RSI item no. 1	0.6 $\pm$ 1.2	1.1 $\pm$ 1.3	0.4 $\pm$ 1.1	0.02‡	—
RSI item no. 7	0.7 $\pm$ 1.1	0.8 $\pm$ 1.1	0.7 $\pm$ 1.1	0.60	—

GERD-HRQL item no. 10: If you take antireflux medication, does this affect your daily life?

RSI item no. 1: Within the last month, how did hoarseness or a problem with your voice affect you? RSI item no. 7: Within the last month, how did troublesome or annoying cough affect you?

\*Wilcoxon rank-sum.

†Linear regression controlling for hernia type, surgery type, recurrence, and preprocedure diagnosis of Barrett's esophagus.

‡Statistically significant.

GERD-HRQL, GERD health-related quality of life; RSI, reflux symptom index.

With age, osteoporosis risk in female patients exceeds that of male patients,<sup>12</sup> and long-term PPI use is associated with an even more profound risk of the disease,<sup>13,14</sup> the effects of which can be devastating.<sup>15,16</sup> Although this is still a low risk relative to the most common diseases threatening female patients today,<sup>17,18</sup> it is our experience that female patients are keenly aware of this particular medication side effect, so much so that it is often the preeminent motivator in their pursuit of an ARP in an effort to stop

or reduce their use of PPIs. In contrast, the conversation around osteoporosis rarely, if ever, occurs in male patients. Although some studies have shown worse outcomes in terms of satisfaction and symptom control,<sup>7,8</sup> the finding that gas and bloat symptoms in particular are worse for female patients is not well studied. The Flatulence After Antireflux Treatment study by Cockbain and colleagues<sup>19</sup> assessed the incidence of increased flatulence after fundoplication in 462 patients and found that excessive flatus

**Table 5.** Linear Mixed Modeling for Responses to GERD-Health-Related Quality of Life Item No. 10: "If You Take Reflux Medication, Does This Affect Your Life?"

Variable	Univariate		Multivariate		Subgroup with FLIP data*	
	Estimate $\pm$ SE	p Value	Estimate $\pm$ SE	p Value	Estimate $\pm$ SE	p Value
Time point						
3 wk vs preprocedure	-0.69 $\pm$ 0.07	<0.01†	-0.69 $\pm$ 0.07	<0.01†	-0.57 $\pm$ 0.13	<0.01†
6 mo vs preprocedure	-0.75 $\pm$ 0.09	<0.01†	-0.76 $\pm$ 0.09	<0.01†	-0.66 $\pm$ 0.15	<0.01†
1 y vs preprocedure	-0.78 $\pm$ 0.07	<0.01†	-0.78 $\pm$ 0.07	<0.01†	-0.80 $\pm$ 0.11	<0.01†
2 y vs preprocedure	-0.58 $\pm$ 0.08	<0.01†	-0.60 $\pm$ 0.08	<0.01†	-0.64 $\pm$ 0.13	<0.01†
5 y vs preprocedure	-0.65 $\pm$ 0.10	<0.01†	-0.67 $\pm$ 0.10	<0.01†	-1.00 $\pm$ 0.72	<0.01†
7 y vs preprocedure	-0.71 $\pm$ 0.12	<0.01†	-0.73 $\pm$ 0.12	<0.01†	—	—
10 y vs preprocedure	-0.57 $\pm$ 0.19	<0.01†	-0.57 $\pm$ 0.19	<0.01†	—	—
Hernia type						
None vs HH/type I	0.05 $\pm$ 0.10	0.59	0.19 $\pm$ 0.13	0.12	0.07 $\pm$ 0.25	0.79
Paraesophageal hernia/type II–IV vs HH/type I	-0.14 $\pm$ 0.07	0.04†	-0.17 $\pm$ 0.07	0.02†	-0.05 $\pm$ 0.12	0.71
Fundoplication type						
Nissen vs Toupet	0.05 $\pm$ 0.07	0.46	0.04 $\pm$ 0.07	0.54	0.09 $\pm$ 0.16	0.55
Recurrence, yes vs no	0.06 $\pm$ 0.11	0.61	0.09 $\pm$ 0.11	0.43	-0.10 $\pm$ 0.26	0.71
Barrett's Esophagus, yes vs no	-0.15 $\pm$ 0.12	0.22	-0.12 $\pm$ 0.12	0.34	-0.08 $\pm$ 0.19	0.69
Intraoperative DI, per unit increase	-0.005 $\pm$ 0.039	0.90	—	—	—	—
Intraoperative DI, $\geq 3$ mm <sup>2</sup> /mmHg	-0.09 $\pm$ 0.11	0.43	—	—	-0.01 $\pm$ 0.12	0.92
Sex, f vs m	0.17 $\pm$ 0.07	0.01†	0.20 $\pm$ 0.07	<0.01†	0.25 $\pm$ 0.12	0.03†

\*Subgroup analysis of patients with intraprocedure FLIP data, N = 322 (patients who underwent antireflux mucosectomy excluded due to missingness of data).

†Statistically significant.

DI, distensibility index; FLIP, functional luminal imaging probe; PEH, paraesophageal hernia.

was reported in 85% of their cohort, with women reporting more gas-related symptoms than men. Assessing these symptoms can be difficult, not least of which because often GERD symptoms, particularly with a concurrent HH or PEH, can include bloating and belching as part of the disease. This is often so reliable that when patients return to clinic after a procedure and state their belching and bloating has returned, we maintain a high suspicion for recurrence. We controlled for recurrence in our analysis for precisely this reason, and yet female patients were still more likely to endorse worse gas and bloat symptoms than male patients out to 1 year postprocedure. The techniques in ARPs do not intentionally vary by sex, which begs the question: is there anatomic or physiologic variation at play? Scapa and colleagues<sup>20</sup> found that esophageal length differs between sexes, with men having longer esophagi, though the clinical impact of this is questionable because esophageal length is also a function of height.<sup>21</sup> Vega and colleagues<sup>22</sup> found that resting LES pressures and the amplitude of the esophageal body contractions on manometry were higher in women compared with men, which may predispose to worse gas and bloat symptoms because a tighter LES does not favor the ability to belch. However, neither of these studies focused on patients who

underwent ARPs, where both the anatomic and physiologic findings have changed drastically from normal baseline. Without clear technical or anatomic and physiologic etiologies for the variation found in our study, our results may reflect social mores in which women may experience heightened social pressure to avoid belching and flatulence relative to men. Female patients may also be more sensitive to increased gas and bloat symptoms relative to male patients because these symptoms are commonly associated with regular menstrual cycles and more regularly experienced by this part of the population.<sup>23,24</sup> However, both of these hypotheses are based on simple assumptions about binary genders and are fraught with gender bias. Socially acceptable behavior is intimately connected to gender, and because our study cannot speak to the gender of the patients who were enrolled, only sex (the gender datapoint was not collected at database inception, nor throughout the study period) we caution the interpretation of these results to mean that all patients who are women should receive heightened warnings regarding the impact of PPIs on their lives and gas and bloat symptoms postprocedurally. Rather, all patients should be asked about their expectations, hopes, and fears surrounding procedural treatment of their GERD, and their perception around

**Table 6.** Linear Mixed Modeling for Gas and Bloat Scores

Variable	Univariate		Multivariate		Subgroup with FLIP data*	
	Estimate ± SE	p Value	Estimate ± SE	p Value	Estimate ± SE	p Value
Time point						
3 wk vs preprocedure	-0.55 ± 0.08	<0.01†	-0.55 ± 0.08	<0.01†	-0.32 ± 0.14	0.03†
6 mo vs preprocedure	-0.51 ± 0.10	<0.01†	-0.51 ± 0.10	<0.01†	-0.38 ± 0.16	0.02†
1 y vs preprocedure	-0.50 ± 0.08	<0.01†	-0.51 ± 0.08	<0.01†	-0.27 ± 0.12	0.03†
2 y vs preprocedure	-0.38 ± 0.09	<0.01†	-0.38 ± 0.09	<0.01†	-0.35 ± 0.14	0.02†
5 y vs preprocedure	-0.55 ± 0.12	<0.01†	-0.58 ± 0.12	<0.01†	-0.73 ± 0.81	0.37
7 y vs preprocedure	-0.64 ± 0.14	<0.01†	-0.68 ± 0.14	<0.01†	—	—
10 y vs preprocedure	-0.62 ± 0.22	<0.01†	-0.69 ± 0.22	<0.01†	—	—
Age, per year increase	-0.01 ± 0.003	<0.01†	-0.01 ± 0.004	<0.01†	-0.02 ± 0.006	0.01†
Hernia type						
None vs HH/type I	-0.12 ± 0.14	0.38	0.24 ± 0.17	0.15	0.01 ± 0.33	0.98
Paraesophageal hernia /type II–IV vs HH/type I	-0.26 ± 0.10	0.01†	-0.30 ± 0.18	0.02†	-0.23 ± 0.17	0.19
Fundoplication type						
Nissen vs Toupet/Dor	0.09 ± 0.10	0.36	0.04 ± 0.10	0.53	0.13 ± 0.21	0.54
Postprocedure proton pump inhibitor use, yes vs no	-0.35 ± 0.13	0.01†	-0.29 ± 0.13	0.03†	0.32 ± 0.22	0.13
Hernia recurrence, yes vs no	0.05 ± 0.15	0.74	0.04 ± 0.15	0.77	-0.12 ± 0.33	0.73
Intraoperative DI, per unit increase	0.001 ± 0.052	0.98	—	—	—	—
Intraoperative DI, ≥3 mm <sup>2</sup> /mmHg	0.04 ± 0.14	0.81	—	—	0.07 ± 0.15	0.64
Sex, f vs m	0.26 ± 0.09	0.01†	0.34 ± 0.09	<0.01†	0.53 ± 0.15	<0.01†

†Statistically significant.

\*Subgroup analysis of patients with intraprocedure FLIP data, N = 322 (patients who underwent antireflux mucosectomy excluded due to missingness of data).

DI, distensibility index; FLIP, functional luminal imaging probe; PEH, paraesophageal hernia.

increased belching, bloating, and flatulence in their lives should be elicited. This will allow clinicians to tailor their discussion to the patient they are working with, regardless of sex or gender.

For clinicians performing ARPs, our findings may again bring up the debate about ideal wrap type. That the patients who underwent Nissen fundoplication were 2.5 times more likely to experience recurrence on multivariate regression is impressive—and is in opposition to many studies that show no difference in recurrence based on wrap type alone.<sup>25,26</sup> This prompted us to include a subgroup analysis in the model such that intraprocedural FLIP data could be considered. The fact that this finding was nullified on subgroup analysis controlling for intraprocedural DI suggests that avoiding recurrence has less to do with the wrap type and more to do with distensibility of the LES complex and crural closure at the conclusion of the procedure. This also speaks volumes to the need for real-time assessment of the LES during the procedure. We were able to define a DI cutoff of 3, above which the risk of recurrence is significantly increased. This finding gives more nuance to the ideal range established by Wu and colleagues<sup>27</sup> of 2.6 to 3.7 mm<sup>2</sup>/

mmHg. As we have shown previously, achieving a DI greater than 3.5 mm<sup>2</sup>/mmHg virtually guarantees no or low postprocedural dysphagia in patients with abnormal motility.<sup>28</sup> However, in this study, a high DI is accompanied by a significant risk of recurrence and so a balance of risks must be struck between that of hernia recurrence vs postprocedure dysphagia. We suggest surgeons tailor their approach based on the patient's clinical data using FLIP in real time, regardless of patient sex. For example, in a young, healthy individual with normal esophageal motility, a DI at the lower end of the range, closer to 2.6 mm<sup>2</sup>/mmHg, strikes the appropriate balance by maximally reducing their lifetime chance of recurrence in exchange for an increased risk of postprocedure dysphagia. Given that the vast majority of patients with postprocedure dysphagia resolve within 1 year, this is likely a reasonable tradeoff. On the other hand, in an older adult with ineffective esophageal motility, tailoring the wrap and crural closure DIs toward the higher end of the spectrum may be a better choice because the lifetime chance of recurrence is lower and the negative impact of postprocedure dysphagia is much higher than for the younger patient.

**Table 7.** Logistic Regression for Recurrence

Variable	Univariate		Multivariate		Subgroup with FLIP data*	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
BMI, per unit increase	0.97 (0.95–1.04)	0.86	0.97 (0.92–1.02)	0.19	0.96 (0.85–1.08)	0.47
Smoking status, current/ former vs never	1.28 (0.82–1.99)	0.29	1.17 (0.74–1.86)	0.49	0.50 (0.16–1.56)	0.23
Hernia type						
None vs HH/type I	1.38 (0.35–5.40)	0.64	3.60 (0.93–143.96)	0.06	3.14 (0.39–25.18)	0.28
Paraesophageal hernia/ type II–IV vs HH/type I	7.54 (3.23–18.17)	<0.01†	6.66 (2.79–15.89)	<0.01†	2.36 (0.61–9.05)	0.21
Operation type						
Nissen vs Toupet	2.44 (1.52–3.92)	<0.01†	2.57 (1.59–4.14)	<0.01†	0.24 (0.02–3.51)	0.30
MSA vs Toupet	0.13 (0.01–2.13)	0.15	0.39 (0.02–6.22)	0.50	1.07 (0.06–19.19)	0.96
ARMS vs Toupet	0.12 (0.01–2.02)	0.14	0.15 (0.01–2.97)	0.21	—	—
Redo procedure, yes vs no	0.92 (0.40–2.13)	0.84	0.83 (0.36–1.95)	0.67	0.22 (0.02–3.37)	0.28
Intraprocedure complication, yes vs no	1.18 (0.37–3.72)	0.78	0.95 (0.29–3.07)	0.93	3.25 (0.44–24.29)	0.25
Intraprocedure DI, per unit increase	1.29 (0.91–1.83)	0.15	—	—	—	—
Intraprocedure DI, $\geq 3$ mm <sup>2</sup> / mmHg	8.15 (1.48–44.90)	0.02†	—	—	7.11 (1.62–31.22)	0.01†
Sex, f vs m	1.73 (1.01–2.96)	0.04†	1.29 (0.74–2.24)	0.37	2.07 (0.59–7.33)	0.26

\*Subgroup analysis of patients with intraprocedure FLIP data, N = 322 (patients who underwent ARMS excluded due to missingness of data).

†Statistically significant.

ARMS, antireflux mucosectomy; DI, distensibility index; FLIP, functional luminal imaging probe; OR, odds ratio; PEH, paraesophageal hernia.

This study has several limitations. First, as stated earlier, our findings can only speak to differences in patients on the basis of sex, not gender, because gender was not a variable collected in our database. Additionally, our standard fundoplication transitioned from Nissen fundoplication to Toupet fundoplication during the study period, which may have affected our results. FLIP measurement of LES pressure instead of bougie use also began during the study period, and arguably changed practice and intraoperative technique. We attempted to minimize this effect by controlling for intraoperative final FLIP measurements on subgroup analysis. Our study was not able to include data on patients' pre- vs postmenopausal states, multiparity, and histories of surgical procedures, such as large ventral hernia repair, abdominoplasty, and diastasis plication—all of which play a role in abdominal wall laxity/tightness—nor the newer antiobesity medications that decrease gastric emptying and may result in bloating and therefore may have confounded our results. Mental health disorders are not collected by our database and may affect ARP outcomes. Because these cluster in women (particularly depression), this may have affected our results as well. As with any survey-based studies, our results are subject to response and nonresponse bias, and missingness of data because

follow-up length has increased affecting our results. Finally, this was a single-institution study, and the majority of the procedures were performed by 1 surgeon. Therefore, these findings may not be applicable to all venues that treat GERD.

## CONCLUSIONS

Female patients have a higher risk of postprocedure gas and bloat symptoms that persist out to 1 year compared with male patients without clear etiology. No statistically significant difference is observed in hernia recurrence or intraoperative FLIP parameters between sexes. Clinicians should discuss the risks of gas and bloat symptoms and how they may affect the quality of life of all patients, regardless of sex or gender.

## Author Contributions

Conceptualization: Zimmermann, Ujiki

Formal analysis: Zimmermann

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