



Systematic Review / Meta-analysis

The new onset of GERD after sleeve gastrectomy: A systematic review

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ABSTRACT

Background: The main adverse effect is gastroesophageal reflux disease (GERD), with concern on the development of Barrett's esophagus and esophageal adenocarcinoma in the long term. However, the relationship between SG and GERD is complex. The aim of this study is to systematically evaluate all published data existing in the literature to evaluate the effect of sleeve gastrectomy on GERD, esophagitis, BE in order to clarify the long-term clinical sequelae of this procedure.

Materials and methods: This systematic review was conducted in accordance with the guidelines for Preferred Reporting Items for Systematic Review. The work has been reported in line with the PRISMA criteria [19]. We evaluated the quality and risk of bias of this Systematic Review using AMSTAR 2 checklist [20]. Published studies that contained outcome data for primary sleeve gastrectomy associated with the primary and secondary outcomes listed below were included. The UIN for [ClinicalTrials.gov](https://clinicaltrials.gov) Protocol Registration and Results System is: NCT05178446 for the Organization UFoggia.

Results: 49 articles were eligible for inclusion that met the following criteria: publications dealing with patients undergoing laparoscopic SG, publications describing pre- and postoperative GERD symptoms and/or esophageal function tests, articles in English, human studies and text complete available.

Conclusions: We have controversial data on LSG and GERD in the literature as there is a multifactorial relationship between LSG and GERD. The most recent studies have shown satisfactory control of postoperative reflux in most patients and low rates of de novo GERD. These data are leading to wider acceptance of LSG as a bariatric procedure even in obese patients with GERD.

1. Introduction

Obesity is classified as one of the most severe global public health problems. Over 2.1 billion adults worldwide are considered overweight or obese; 640 million of these are classified as obese. Sleeve gastrectomy (SG) has become the most common procedure performed in the world since 2014 [1] because it is well defined, it is easier to perform than other types of bariatric surgery, the learning curve is shorter, the morbidity and mortality rates are low, and it leads to effective weight loss [2]. Obese patients develop obesity-related comorbidities including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, coronary artery disease, certain types of cancer, and gastroesophageal reflux disease (GERD) [3–7]. The main adverse effect is gastroesophageal reflux disease (GERD), with concern on the development of Barrett's esophagus and esophageal adenocarcinoma in the long term. However,

the relationship between SG and GERD is complex [8–12]. Different mechanisms involved: disruption of the angle of His, partial sectioning of sling fibers of the lower esophageal sphincter (LES), reduced gastric compliance due to gastric fundus removal, occurrence of hiatal hernia (HH), or reduced antral function. In contrast, other studies have reported a decreased prevalence of GERD after SG [13–15] explained by several mechanisms including weight loss, decreased acid production and accelerated gastric emptying. The measured increase in GERD prevalence ranged from 2.1% to 34.9% in the analyzed literature. There was marked heterogeneity between the studies in regard to a number of factors including preoperative BMI, method of evaluating GERD, exclusion criteria, length of follow-up, and operative technique [16–18] [–] [18].(see [fig 1](#))

The aim of this study is to systematically evaluate all published data existing in the literature to evaluate the effect of sleeve gastrectomy on

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GERD, esophagitis, BE in order to clarify the long-term clinical sequelae of this procedure.

2. Materials and methods

This systematic review was conducted in accordance with the guidelines for Preferred Reporting Items for Systematic Review. The work has been reported in line with the PRISMA 2020 criteria [19].

We evaluated the quality and risk of bias of this Systematic Review using AMSTAR 2 checklist [20].

A systematic search was performed using electronic searches in EMBASE, Medline, Cochrane Library, and Psychinfo. Free text search in all fields was performed for "Sleeve Gastrectomy", "Bariatric Surgery", "Obesity", "Gastrectomy", "Gastric Sleeve", "Stomach Staple", "Gastro-esophageal Reflux", "Gastro - Esophageal reflux", "Reflux", "Metaplasia", "Barrett's esophagus" and "Barrett's esophagus". The search included all study designs, with additional non-research captured studies identified through bibliographic cross-references.

Published studies that contained outcome data for primary sleeve gastrectomy associated with the primary and secondary outcomes listed below were included.

The UIN for [ClinicalTrial.gov](https://clinicaltrials.gov) Protocol Registration and Results System is: NCT05178446 for the Organization UFoggia (<https://clinicaltrials.gov/ct2/show/NCT05178446>).

3. Results

Figure (PRISMA Flow Chart) shows the study selection flowchart. Through the literature search, we identified 707 citations. We removed any duplicates and were left with 120 references. After excluding irrelevant reports by reviewing titles and abstracts, we then retrieved 73 full-text articles that were eligible. There were 8 articles with unrelated topics, 2 without full text, 9 conference abstracts, and 5 non-English/Chinese literatures excluded. Ultimately, 49 original articles were included, as shown in the study flowchart (Table 1). [22–69].

4. Discussion

Obesity is one of the risk factors for GERD, which has resulted in a significant increase in the incidence of GERD worldwide [70].

Obesity has been reported to increase the incidence of GERD with an OR of 1.73 and Barrett's esophagus with an OR of 1.24; esophageal adenocarcinoma is the most serious complication of GERD (OR, 2.45) [71,72].

Numerous studies have been performed in the literature with controversial results on the onset of GERD after LSG.

Albanopoulos et al., Alexandrou et al. and Althuwaini et al. [22,23] showed that LSG seemed to precipitate GERD symptoms, dissection near the angle of His, and drastic reduction in gastric capacity increased the chance that patients would maintain or develop new GERD symptoms.

The studies by Arman et al., Borbely et al. and Braghetto et al. [26, 30,32] found that LSG is associated with a significantly higher

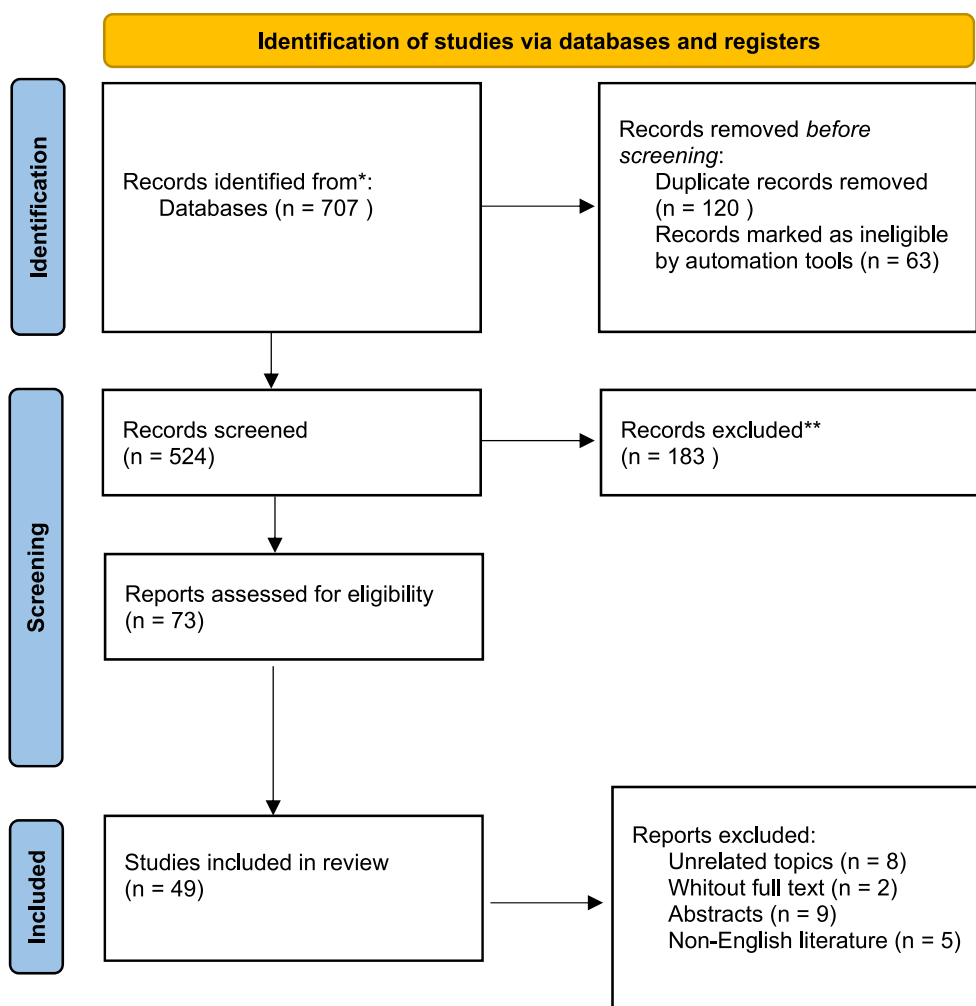


Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Table 1
Systematic review.

Investigators Table 1: Systematic Review	Title of study	Year	Patients (n)	Preoperative BMI (kg/m ²)	Reflux evaluation	Follow- up (mo)	GERD (%)		Bougie size (F)
							Preoperative	Postoperative	
M.E. Abd Ellatif et al. [16]	Long term predictors of success after laparoscopic sleeve gastrectomy	2014	1395	46	Upper GI endoscopy	84		11.4	<36 (837) - >44 (558)
Albanopoulos et al. [17]	The impact of laparoscopic sleeve gastrectomy on weight loss and obesity-associated comorbidities: the results of 3 years of follow up	2016	88	47.8	Symptoms	36	27	9.2	34
Alexandrou et al. [18]	Laparoscopic sleeve gastrectomy for morbid obesity: 5 year results	2015	30	55.5 ± 1.7	Esofagogastroscopy	60		16	29
Althuwaini et al. [19]	Prevalence and predictors of gastroesophageal reflux disease after laparoscopic sleeve gastrectomy	2018	213	47,84	GERD-Health-Related-Quality of Life questionnaire	12		47%	32
Angrisani et al. [20]	Five year results of laparoscopic sleeve gastrectomy: effects on gastroesophageal reflux disease symptoms and co- morbidities	2016	105	group1: <50; group2:>50	symptoms, gastrointestinal endoscopy, double contrast barium swallow	60	group 1: 31% group 2: 25%	group 1: 18,2% group: 20%	40
Arman et al. [21]	Long-term (11+years) outcomes in weight patient satisfaction, comorbidities, and gastroesophageal reflux treatment after laparoscopic sleeve gastrectomy	2016	110	38,8	medication use	132	11.1	21.4	34
Barr et al. [22]	GERD and acid reduction medication use following gastric bypass and sleeve gastrectomy	2017	147	49.1 ± 8	acid reduction medication (ARM) utilization, Gastroesophageal reflux disease health-related quality of life (GERD-HRQL)	12	N.R.	N.R.	36–40
Barry et al. [23]	Laparoscopic vertical sleeve gastrectomy: a 5 year veterans affairs review	2017	223	45.4 (from 33 to 56.6)	medication use	60	56	13	34
Berry et al. [24]	Sleeve gastrectomy outcomes in patients with BMI between 30 and 35- 3 years of follow-up	2018	252	32.3 (30–35)	gastrointestinal endoscopy, barium esophagogram, esophageal manometry, esophageal pH test	36	25,43	64,6 improvement of their symptoms - 2.4 de novo symptoms	36
Borbely et al. [25]	De novo gastroesophageal reflux disease after sleeve gastrectomy: role of preoperative silent reflux	2018	222	49.6 ± 7.2	questionnaires, upper endoscopy, 24 h-pH manometry, esophagogram, medication use	32	25 silent GERD preop - 23 with preoperative diagnosis of GERD	52	32
Boza et al. [26]	Long-term outcomes of laparoscopic sleeve gastrectomy as a primary bariatric procedure	2014	161	34.9 (33.3–37.5)	GERD symptoms questionnaires, endoscopy	60	4.3	26.7	60
Braghetto et al. [27]	Prevalence of Barrett's esophagus in bariatric patients	2016	231	38.4 + 3.1	clinical evaluation, Endoscopy	60	0 (patients with GERD didn't	23.2	34

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Table 1 (continued)

Investigators Table 1: Systematic Review	Title of study	Year	Patients (n)	Preoperative BMI (kg/m ²)	Reflux evaluation	Follow- up (mo)	GERD (%)		Bougie size (F)
							Preoperative	Postoperative	
	undergoing sleeve gastrectomy						undergo sleeve gastrectomy)		
Braghetto et al. [28]	Late esophagogastric anatomic and functional changes after sleeve gastrectomy and its clinical consequences with regards to gastroesophageal reflux disease	2019	248	38.4 ± 3,4	reflux symptoms and Upper gastrointestinal ednoscopy	60	0	65,1	N.R.
Burgerhart et al. [29]	Effect of sleeve gastrectomy on gastroesophageal reflux	2014	20	47.6 ± 6.1	esophageal function tests (high resolution manometry and 24-h pH impedance metry); reflux disease questionnaire	3	70	20	34
Carabotti et al. [30]	Impact of laparoscopic sleeve gastrectomy on upper gastrointestinal symptoms	2013	97	respondent patients: 45.9; non respondent patients: 43.3	questionnaire for upper GI symptoms following Roma III criteria	13	27	25,67	42
Carter et al. [31]	Association between gastroesophageal reflux disease and laparoscopic sleeve gastrectomy	2011	206	46.6	symptoms, medication use, upper gastrointestinal radiography	24	34.6	49 complained of immediate GERD symptoms; 47.2had persistent GERD symptoms that lasted >1 month after LSG; 33.8% were taking medication specifically for GERD after LSG	34
Castagneto Gissey et al. [32]	10-year follow-up after laparoscopic sleeve gastrectomy: outcomes in a monocentric series	2018	182	46.6 ± 7.3	clinical symptomatology referred by patients on a symptom assessment scale, esophagogastroduodenoscopy if necessary	120	18.9	42.9	48
Catheline et al. [33]	Five year results of sleeve gastrectomy	2013	65	49.9 ± 9.1 range (35.7–71.8)	PPI medication, symptoms, endoscopy	60	11.1	33.3	34
Chuffart et al. [34]	Long-term results after sleeve gastrectomy for gastroesophageal reflux disease: a single-center French study	2017	64	47 ± 8	upper GI endoscopy, symptoms, medication (PPI)	72	26.8	42	36
Coupaye et al. [35]	Gastroesophageal reflux after sleeve gastrectomy: a prospective mechanistic study	2018	119	43.3 ± 5.7	HRM(high-resolution esophageal manometry), APM (ambulatory 24-h esophageal pH monitoring), upper endoscopy	12	34	52 (patients without preoperative GERD); 56,25 (patients with preoperative GERD)	36
Dakour Aridi et al. [36]	Gastroesophageal reflux disease after laparoscopic sleeve gastrectomy with concomitant hiatal hernia repair: an unresolved question	2017	165	44.1 ± 10.7 (LSG), 42.7 ± 15.3 (LSG + HHR)	symptoms, PPI use	24	41.6 (LSG) 61.8 (LSG + HHR)	46.2 (LSG) - 41.4 (LSG + HHR)	36/40
Del Genio et al. [37]	Sleeve Gastrectomy and development of "de novo" gastroesophageal reflux	2014	25	46.1 (38–58)	multichannel intraluminal impedance and pH (MII-pH), High-resolution manometry with impedance (HRiM), questionnaire	13 (11–17)	N.R.	N.R.	40
DuPree et al. [38]	Laparoscopic sleeve gastrectomy in	2014	4832	47.9	REflux symptoms and Upper gastrointestinal ednoscopy	6	44.5		N.R.

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Table 1 (continued)

Investigators Table 1: Systematic Review	Title of study	Year	Patients (n)	Preoperative BMI (kg/m ²)	Reflux evaluation	Follow- up (mo)	GERD (%)		Bougie size (F)
							Preoperative	Postoperative	
	patients with preexisting Gastroesophageal Reflux disease. A National Analysis							84.1 continued to have GERD symptoms	
Felsenreich et al. [39]	Update: 10 years of sleeve gastrectomy—the first 103 patients	2018	103	49 ± 9.1	gastrosopies, manometries, 24-h pH metries, reflux symptom index questionnaire	120	N.R.	57	N.R.
DM Felsenreich et al. [40]	Reflux, Sleeve Dilation, and Barret's Esophagus after Laparoscopic Sleeve Gastrectomy: Long-Term Follow-Up	2017	43	49.5 ± 9,6	Reflux symptoms and Upper gastrointestinal ednoscopy	129	0	38	42–48
Flolo et al. [41]	Five-year outcomes after vertical sleeve gastrectomy for severe obesity: a prospective cohort study	2017	168	46.2 ± 6.4	symptoms, medication use	60	12	35	32
Gadiot et al. [42]	Long-term results of laparoscopic sleeve gastrectomy for morbid obesity: 5 to 8-year results	2017	277	44.8 ± 6.7	symptoms	60	10.1	7 (9pz)	N.R.
Garg et al. [43]	Mid to long term outcomes of laparoscopic sleeve gastrectomy in Indian population: 3–7 years results - a retrospective cohort study	2017	424	46.67 ± 15.8	upper gastrointestinal endoscopy, GERD severity symptom questionnaire, PPI intake	60	16.5	2.8	36
Gemici et al. [44]	Outcomes of laparoscopic sleeve gastrectomy by means of esophageal manometry and pH-metry, before and after surgery	2020	62	47.91 ± 6.23	Upper gastrointestinal endoscopy, 24 h pH-monitoring (APM), Esophageal manometry (EM)	36	N.R.	N.R.	36
Genco et al. [45]	Gastroesophageal reflux disease and Barret's esophagus after laparoscopic sleeve gastrectomy: a possible, underestimated long-term complication	2017	162	45.8 ± 6.3	visual analogue scale (VAS) evaluation of GERD symptoms, PPIs consumption recording, esophagogastrroduodenoscopy (EGD)	58	33.6	68.1	48
Georgia et al. [46]	24-h multichannel intraluminal impedance PH-metry 1 year after laparoscopic sleeve gastrectomy: an objective assessment of gastroesophageal reflux disease	2017	12	48.97	24-h multichannel intraluminal impedance-pH metry (MIIPH) pre-and 12 months post-LSG; symptoms; EGD	12	42.06.00	83.33	38
Hendricks et al. [47]	Impact of sleeve gastrectomy on gastroesophageal reflux disease in a morbidly obese population undergoing bariatric surgery	2016	919	N.R.	symptoms, PPI treatment, upper gastrointestinal endoscopy (UGI), esophagogastrroduodenoscopy (EGD), pH manometry	24	group B 1% (13)	group A 3% (25)	38
Himpens et al. [48]	Long-term results of laparoscopic sleeve	2010	53	39 (range, 31–57; SD, 5.4)	Bariatric analysis and reporting outcome system (BAROS) score	72	3.3	23	34

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Table 1 (continued)

Investigators Table 1: Systematic Review	Title of study	Year	Patients (n)	Preoperative BMI (kg/m ²)	Reflux evaluation	Follow- up (mo)	GERD (%)		Bougie size (F)
							Preoperative	Postoperative	
Hirth et al. [49]	gastrectomy for obesity Laparoscopic sleeve gastrectomy: long-term weight loss outcomes	2015	16	43.5	medications, symptoms	84	35	35	32
Howard et al. [50]	Gastroesophageal reflux after sleeve gastrectomy in morbidly obese patients	2011	28	55.5 range (39–80)	upper gastrointestinal radiographic swallow study, GERD score questionnaire, symptoms, medication use	32	25	39	38
Kehagias et al. [51]	Efficacy of sleeve gastrectomy as sole procedure in patients with clinically severe obesity (BMI <50 kg/m ²)	2013	203	43.2 ± 2.8	PPI prescription	36	0	7.4	32
Kowalewski et al. [52]	Long-term outcomes of laparoscopic sleeve gastrectomy—a single-center, retrospective study	2018	84	51.6	typical symptoms, PPI therapy	96	N.R.	60	36
Lemaitre et al. [53]	Laparoscopic sleeve gastrectomy in the South Pacific. Retrospective evaluation of 510 patients in a single institution	2016	384	47.8 ± 7.8	PPI therapy, endoscopic diagnosis, symptoms	24	N.R.	9.4	33
Lim et al. [54]	Correlation between symptomatic gastro-esophageal reflux disease (GERD) and erosive esophagitis (EE) post vertical sleeve gastrectomy (VSG)	2019	63	42.1 ± 1.2	questionnaire that included documentation of reflux symptomatology, medication use; EGD	13	31.7	47.6	36
Menekos et al. [55]	Laparoscopic sleeve gastrectomy performed with intent to treat morbid obesity: a prospective single-center study of 261 patients with a median follow-up of 1 year	2010	261	45.2 (range 32.1–72.7)	upper gastrointestinal endoscopy	12	N.R.	25	38
Nocca et al. [56]	Five-year results of laparoscopic sleeve gastrectomy for the treatment of severe obesity	2017	1050	44.58 ± 7.71	symptoms	60	21.27	39.1	36
Pilone et al. [57]	Gastroesophageal reflux after sleeve gastrectomy: new onset and effect on symptoms on a prospective evaluation	2019	104	44.2 ± 4.2	GERD-HRQL questionnaire, EGDS, PPI use	12	27.9	10.6	32
Pok et al. [58]	Laparoscopic sleeve gastrectomy in Asia: long term outcome and revisional surgery	2016	61	37.3 ± 8.1 (range 20.8–75.3)	symptoms	60	N.R.	17	36
Rawlins et al. [59]	Sleeve gastrectomy 5 year outcomes of a single institution	2013	49	65 (range 39–106)	patient report	60	N.R.	11	26.4
Rebecchi et al. [60]	Gastroesophageal reflux disease and laparoscopic sleeve	2014	71	44.3 ± 3.8	gastroesophageal reflux disease symptom assessment scale (GSAS), esophageal manometry	48	group A: 42.3 group B: 0	group A: symptoms	36

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Table 1 (continued)

Investigators Table 1: Systematic Review	Title of study	Year	Patients (n)	Preoperative BMI (kg/m ²)	Reflux evaluation	Follow- up (mo)	GERD (%)		Bougie size (F)
							Preoperative	Postoperative	
Sharma et al. [61]	gastrectomy: a physiopathologic evaluation Evaluation of gastroesophageal reflux before and after sleeve gastrectomy using symptom scoring, scintigraphy, and endoscopy	2014	32	47.8	and 24-h pH monitoring, DeMeester composite reflux score Carlsson Dent Questionnaire and GERD questionnaire to assess Symptom-Severity score, upper GI endoscopy, radionuclide scintigraphy	12	6.25 (2pz)	78.1	improved group B: 5.4 36
Sheppard et al. [62]	Rates of reflux before and after laparoscopic sleeve gastrectomy for severe obesity	2015	205	48.5 ± 9.7	symptoms, medication use	12	25.5	58 increased PPI - 42 continued the same treatment - 0 decreased	50
Soricelli et al. [63]	Lack of correlation between gastroesophageal reflux disease symptoms and esophageal lesions after sleeve gastrectomy	2018	219	46.2 ± 7.2	EGD, VAS evaluation of GERD symptoms, PPI consumption	66	40.9	70.2	48
Viscido et al. [64]	Laparoscopic sleeve gastrectomy: endoscopic findings and gastroesophageal reflux symptoms at 18-month follow-up	2018	109	47.8 ± 16	questionnaire, GERD symptoms, EGD	18	33	44	42

likelihood that acid-lowering medications are needed to control GERD symptoms 12 months after LSG compared with gastric bypass. LSG leads to a considerable rate of postoperative GERD. De novo GERD consist of approximately half of preoperative silent GERD and completely de novo GERD. Most patients with preoperative silent GERD have become symptomatic after LSG. Barrett's esophagus could be a late complication after SG and bariatric surgeons should be aware of the important association between GERD and obesity.

Burgerhart et al. [34] confirm that it seems likely that the increase in acid exposure after LSG is due to the modified anatomy, which leads to a decrease in the resting pressure of Les. The study results support the idea that in patients with significant preoperative symptoms of GERD, gastric bypass surgery may be more appropriate than LSG.

Del Genio et al. and DuPree et al. [42,43] claim that LSG is an effective restrictive procedure that creates delayed esophageal emptying without compromising the function of the LES. Retrograde movements and increased acid exposure are likely due to postprandial stasis and regurgitation. LSG did not reliably relieve or improve GERD symptoms and induced GERD in some previously asymptomatic patients.

Indeed, Flolo et al. [46] confirmed that the incidence of GERD more than doubled from baseline at 2 years and further increased at a rate of 35% at 5 years.

De novo gastroesophageal reflux symptoms appear between the third and sixth postoperative year. This unfavorable evolution may have been prevented in some patients by continuous follow-up outpatient visits beyond the third year.

The new onset of postoperative GERD is an unfortunate side effect of LSG, and more studies reflecting the aggressive closure of healing defects are needed to determine if this provides a long-term solution to this problem.

LSG can increase the prevalence of GERD despite satisfactory weight loss.

In the study by Menenakos et al. [60] about 25% of patients

developed or worsened their GERD symptoms, all responsive to PPI treatment (65 out of 261 patients). Heartburn was significantly relieved after the postoperative first trimester. Symptoms of GERD are especially common in the first few months. Gastroesophageal reflux is the main complication. Proton pump inhibitor treatment is mostly effective in controlling patients' symptoms. Endoscopic surveillance is desirable in the long term for these patients.

Rebecchi et al. and Sharma et al. [65,66] concluded that in obese patients with GERD, LSG improves symptoms and controls reflux in most cases, whereas in patients with no preoperative evidence of GERD, de novo reflux is rare. Therefore, LSG should be considered an effective option for the surgical treatment of obese patients with GERD. The presence of GERD cannot be considered a contraindication to sleeve gastrectomy. There is improvement in GERD as assessed by the symptom questionnaires. The new onset of GERD detected on scintigraphy may not be pathological as there is a decrease in total acid production after surgery; however, it still remains an important issue and needs long-term follow-up [74–76].

The limitations of this study are high heterogeneity and no data from randomized controlled trials. Several studies had varying selection criteria when offering surgery to people with and without GERD. There was a lack of data on the standardization of surgical technique. The follow-up time interval was variable, and long-term subgroup analysis was performed in an attempt to compensate for this. Some studies aimed to study reflux specifically, while others reported it as secondary outcomes. Studies using physiological and invasive techniques to investigate GERD have found higher rates than those using symptomatology alone.

5. Conclusions

We have controversial data on LSG and GERD in the literature as there is a multifactorial relationship between LSG and GERD. The most

recent studies have shown satisfactory control of postoperative reflux in most patients and low rates of de novo GERD. Compared to LSG, obese patients receiving LRYGB had a lower risk of new onset or worsening of GERD. Some patients have been converted to LRYGB treatment due to severe reflux after LSG. Therefore, we recommend LRYGB as the preferred treatment for obese patients with GERD.

These data are leading to wider acceptance of LSG as a bariatric procedure even in obese patients with GERD, provided a tubular cuff is created, as recently stated in the 5th International Consensus Conference on sleeve gastrectomy [73].

In conclusion, bariatric surgery has become safer as surgeons gain experience in evaluating and treating obese patients, but careful medical evaluation is mandatory before choosing the type of bariatric surgery, especially for those patients who already have GERD.

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Ethical approval

The ethics committee of our institution approved the study.

Consent

Informed consent was obtained from all individual participants included in the study.

Author contribution

NICOLA TARTAGLIA and GIOVANNA PAVONE performed the study conception and design.

ALESSANDRO PORFIDO analyzed and interpreted the data.

MARIO PACILLI and PIERCARMINE PANZERA contributed to acquisition of the data.

ANTONIO AMBROSI revised the manuscript.

Trial registry number

1. Name of the registry: [ClinicalTrials.gov](https://clinicaltrials.gov)
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Guarantor

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Declaration of competing interest

GIOVANNA PAVONE, NICOLA TARTAGLIA, ALESSANDRO PORFIDO, PIERCARMINE PANZERA, MARIO PACILLI, ANTONIO AMBROSI declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.103584>.

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