

Incidence of Barrett's esophagus and esophageal cancer following sleeve gastrectomy versus liraglutide therapy

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Abstract

Background Sleeve gastrectomy has consistently been linked to gastroesophageal reflux disease and Barrett's esophagus. At the same time, the long-term effects of glucagon-like peptide-1 receptor agonists, particularly short-acting agents such as liraglutide, are less well understood. We compared the incidence of Barrett's esophagus and esophageal cancer among patients treated with liraglutide vs. those who underwent sleeve gastrectomy.

Methods We conducted a retrospective cohort study using a large electronic health record database. Adults with obesity treated with liraglutide were compared to those who underwent sleeve gastrectomy. Propensity score matching was used to balance demographics, comorbidities, medication use and body mass index. The primary outcome was the incidence of Barrett's esophagus without dysplasia diagnosed 3 years or more after treatment. Secondary outcomes involved esophageal cancer and Barrett's esophagus with dysplasia. Risk ratios (RR) and 95% confidence intervals (CI) were calculated.

Results We analyzed 10,048 sleeve gastrectomy and 10,048 liraglutide patients. Barrett's esophagus without dysplasia was more frequent in the sleeve (0.3%) than in the liraglutide (0.1%) group, with a risk difference of 0.2% (95%CI 0.1-0.3%) and RR 2.70 (95%CI 1.31-5.56). Barrett's esophagus with dysplasia was also more common in the sleeve group (0.1% vs. 0%). No significant difference in esophageal cancer was observed.

Conclusions Sleeve gastrectomy is associated with a higher risk of Barrett's esophagus compared to liraglutide, though esophageal cancer rates did not differ. Liraglutide may offer a safe option for patients at risk of esophageal complications.

Keywords Barrett's esophagus, cancer, liraglutide, sleeve, obesity

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Introduction

Obesity is a well-established risk factor for gastroesophageal reflux disease (GERD), Barrett's esophagus and esophageal cancer [1,2]. As the prevalence of obesity continues to rise, particularly among younger populations and women of childbearing age [3,4], the need for effective and safe weight-loss interventions becomes increasingly urgent. Among these strategies, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sleeve gastrectomy have become 2 of the most utilized and effective options [5-7].

GLP-1 RAs have been an area of concern in some newer studies, regarding their effects on the gastrointestinal system. Short-acting GLP-RAs have been independently linked to an increased risk of Barrett's esophagus and GERD in an article in *Gut* [8]. Liraglutide is characterized as a short-acting GLP-1 RA, as it is dosed once a day [9]. Semaglutide is dosed once a week and has a pharmacokinetic profile unlike

that of liraglutide [10]. This can change acid exposure to the esophagus and gastrointestinal motility, resulting in differences in how reflux-related conditions develop [11,12].

Sleeve gastrectomy permanently changes the anatomy of the gastrointestinal tract, leading to higher levels of post-surgical complications such as Barrett's esophagus and postoperative GERD [13,14]. In patients with ongoing symptoms or structural problems, such as stenosis or torsion, surgical revision may be needed [15-17].

Given the increasing use of both therapies, a direct comparison of long-term esophageal outcomes is clinically relevant. This study's goal was to evaluate the incidence of Barrett's esophagus, with and without dysplasia, as well as esophageal malignancy, among patients treated with liraglutide vs. those who underwent sleeve gastrectomy. We utilized a robust database to explore other important clinical inquiries, such as reversibility, long-term weight maintenance, accessibility and reproductive safety [18-21]. The findings of this study will contribute to informed personalized decision making in the management of obesity.

Patients and methods

Study design and data source

A retrospective cohort study was performed using the TriNetX Research Network. This system pulls together de-identified and Health Insurance Portability and Accountability Act (HIPAA)-compliant electronic health record data, including longitudinal information on demographics, diagnoses, procedures, medications and laboratory values, from healthcare organizations throughout the United States. Because the data are de-identified and HIPAA-compliant, institutional review board approval was not required.

Study population and cohort definitions

Two exposure cohorts were identified: (1) patients prescribed liraglutide and (2) patients who underwent sleeve gastrectomy. The cohort selection period extended from January 1, 2015, to January 1, 2022, to ensure that all patients had a minimum potential follow-up time of 3 years before the end of the study period on January 1, 2025. Eligible patients were aged ≥ 18 years, with a documented diagnosis of obesity (ICD-10 code E66) prior to the index event, and comprised 2 cohorts.

- Liraglutide cohort: Patients with at least 1 recorded prescription for liraglutide (identified via RxNorm codes) followed by at least 1 recorded prescription 3 years later and no prior sleeve gastrectomy.
- Sleeve gastrectomy cohort: Patients who underwent sleeve gastrectomy, as identified by CPT code 43775 or ICD-10-PCS procedural code 0DB64Z3, and did not have any prescription for liraglutide (identified via RxNorm codes).

For the liraglutide cohort, the index date was the second recorded prescription occurring at least 3 years after the first, to ensure long-term exposure; for the sleeve gastrectomy cohort, it was the date of the first documented procedure. Patients with a recorded diagnosis of Barrett's esophagus (ICD-10 code K22.7) or esophageal cancer (ICD-10 code C15.9) prior to the index date were excluded, to ensure only incident cases were assessed. Additional exclusions included any incomplete demographic or follow-up data.

Outcome measure

The primary outcome was the difference between the 2 cohorts in rates of newly diagnosed Barrett's esophagus without dysplasia, occurring at least 3 years after the index event. Barrett's esophagus without dysplasia was identified via ICD-10-CM diagnosis code K22.70. Patients were followed from the index date to the earliest of the following: diagnosis of Barrett's esophagus, death, loss to follow up, or end of the outcomes study period (January 1, 2025). Secondary outcomes included the incidence of Barrett's esophagus with dysplasia (identified via ICD-10-CM diagnosis code K22.719) and esophageal malignancy (identified via ICD-10-CM diagnosis code C15.9), also occurring at least 3 years post-index. Similar follow-up censoring criteria applied.

Propensity score matching

To reduce confounding and selection bias, 1:1 propensity score matching was performed using a greedy nearest-neighbor algorithm without replacement and a caliper of 0.1 pooled standard deviations of the logit of the propensity score. Propensity score matching was performed on 37 characteristics. In the Demographics category patients were matched on the following: Age at Index, Female, Male, Unknown Gender, Not Hispanic or Latino, Unknown Ethnicity, Hispanic or Latino, White, Black or African American, Unknown Race, Other Race, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander. In the Diagnosis category patients were matched on Diabetes mellitus, Hypertensive diseases, Sleep apnea, Disorders of lipoprotein metabolism and other lipidemias, Fatty (change of) liver, not elsewhere classified, Metabolic syndrome and other insulin resistance, Tobacco use, Gastroesophageal reflux disease, Ischemic heart diseases, Heart failure, Alcohol-related disorders and Cerebrovascular disease. In the Medication category patients were matched on omeprazole, pantoprazole, esomeprazole, lansoprazole, dexlansoprazole, dulaglutide, semaglutide, lixisenatide, tirzepatide and exenatide. In the Laboratory category patients were matched on body mass index (BMI). Characteristics of the cohorts before and after matching are summarized in Table 1. Covariate balance was assessed using standardized mean differences (SMDs), with SMDs < 0.1 indicating adequate balance.

Table 1 Baseline characteristics of patients in the sleeve gastrectomy cohort compared to those in the liraglutide cohort before and after propensity score matching

Characteristic	Before matching			After matching				
	Sleeve gastrectomy (N=39,518)	Liraglutide (N=29,477)	SMD	P-Value	Sleeve Gastrectomy (N=10048)	Liraglutide (N=10048)	SMD	P-Value
Demographics								
Age at index (mean±SD)	43.1±12.4	58.0±12.8	1.178	<0.001	51.4±11.2	51.2±12.9	0.015	0.292
Female, n (%)	29,952 (75.8%)	18,553 (62.9%)	0.282	<0.001	7058 (70.2%)	6977 (69.4%)	0.018	0.213
Black or African American, n (%)	8717 (22.1%)	5,539 (18.8%)	0.081	<0.001	2144 (21.3%)	2154 (21.4%)	0.002	0.863
Male, n (%)	7162 (18.1%)	9,869 (33.5%)	0.357	<0.001	2596 (25.8%)	2642 (26.3%)	0.010	0.460
White, n (%)	23,999 (60.7%)	19,708 (66.9%)	0.128	<0.001	6447 (64.2%)	6440 (64.1%)	0.001	0.918
Unknown race, n (%)	4944 (12.5%)	2658 (9.0%)	0.113	<0.001	999 (9.9%)	1021 (10.2%)	0.007	0.606
Hispanic or Latino, n (%)	4968 (12.6%)	2422 (8.2%)	0.143	<0.001	947 (9.4%)	993 (9.9%)	0.016	0.272
Diagnosis								
Diabetes mellitus, n (%)	10,187 (25.8%)	25,161 (85.4%)	1.498	<0.001	7057 (70.2%)	6954 (69.2%)	0.022	0.114
Hypertensive diseases, n (%)	21,276 (53.8%)	24,612 (83.5%)	0.675	<0.001	7425 (73.9%)	7402 (73.7%)	0.005	0.712
Sleep apnea, n (%)	19,329 (48.9%)	13,160 (44.6%)	0.086	<0.001	5140 (51.2%)	5142 (51.2%)	<0.001	0.977
Hyperlipidemia, n (%)	11,985 (30.3%)	21,195 (71.9%)	0.915	<0.001	5661 (56.3%)	5678 (56.5%)	0.003	0.809
Disorders of lipoprotein metabolism, n (%)	15,362 (38.9%)	24,440 (82.9%)	1.011	<0.001	6890 (68.6%)	6848 (68.2%)	0.009	0.524
Fatty liver, n (%)	4541 (11.5%)	5378 (18.2%)	0.191	<0.001	1664 (16.6%)	1629 (16.2%)	0.009	0.505
Metabolic syndrome, n (%)	1681 (4.3%)	2569 (8.7%)	0.182	<0.001	723 (7.2%)	721 (7.2%)	0.001	0.956
Tobacco use, n (%)	1660 (4.2%)	2211 (7.5%)	0.141	<0.001	597 (5.9%)	561 (5.6%)	0.015	0.276
GERD, n (%)	19,738 (49.9%)	13,583 (46.1%)	0.077	<0.001	4938 (49.1%)	4889 (48.7%)	0.010	0.489
Ischemic heart diseases, n (%)	2927 (7.4%)	8093 (27.5%)	0.548	<0.001	1692 (16.8%)	1671 (16.6%)	0.006	0.691
Heart failure, n (%)	1725 (4.4%)	4660 (15.8%)	0.387	<0.001	984 (9.8%)	964 (9.6%)	0.007	0.633
Alcohol related disorders, n (%)	747 (1.9%)	1093 (3.7%)	0.110	<0.001	275 (2.7%)	304 (3.0%)	0.017	0.221
Cerebrovascular diseases, n (%)	1003 (2.5%)	3883 (13.2%)	0.403	<0.001	597 (5.9%)	601 (6.0%)	0.002	0.905
Medication								
Omeprazole, n (%)	12,985 (32.9%)	9941 (33.7%)	0.018	0.017	3400 (33.8%)	3447 (34.3%)	0.010	0.484
Pantoprazole, n (%)	7528 (19.0%)	9347 (31.7%)	0.294	<0.001	2622 (26.1%)	2574 (25.6%)	0.011	0.439
Esomeprazole, n (%)	1899 (4.8%)	3793 (12.9%)	0.287	<0.001	919 (9.1%)	897 (8.9%)	0.008	0.588
Lansoprazole, n (%)	1395 (3.5%)	1332 (4.5%)	0.050	<0.001	412 (4.1%)	403 (4.0%)	0.005	0.748
Dexlansoprazole, n (%)	192 (0.5%)	526 (1.8%)	0.123	<0.001	106 (1.1%)	110 (1.1%)	0.004	0.784
Dulaglutide, n (%)	684 (1.7%)	4079 (13.8%)	0.464	<0.001	590 (5.9%)	651 (6.5%)	0.025	0.074
Semaglutide, n (%)	360 (0.9%)	4677 (15.9%)	0.560	<0.001	348 (3.5%)	479 (4.8%)	0.066	<0.001
Lixisenatide, n (%)	20 (0.1%)	196 (0.7%)	0.103	<0.001	19 (0.2%)	19 (0.2%)	<0.001	>0.99
Tirzepatide, n (%)	10 (0.0%)	1047 (3.6%)	0.268	<0.001	10 (0.1%)	28 (0.3%)	0.041	0.003
Exenatide, n (%)	281 (0.7%)	3723 (12.6%)	0.492	<0.001	270 (2.7%)	290 (2.9%)	0.012	0.391
Laboratory								
BMI (mean±SD)	45.8±7.2	37.9±7.9	1.047	<0.001	45.1±7.3	39.3±8.3	0.742	<0.001

SMD, standardized mean difference; SD, standard deviation; GERD, gastroesophageal reflux disease; BMI, body mass index

Statistical analysis

Descriptive statistics summarized baseline characteristics before and after matching. Continuous variables were reported as means with standard deviations, or medians with interquartile ranges; categorical variables were reported as frequencies and percentages. Incidence rates of Barrett's esophagus and esophageal malignancy diagnosed ≥ 3 years post-index were calculated for each group, and risk ratios (RRs) with 95% confidence intervals (CIs) were used to compare outcomes between cohorts. All analyses were conducted using TriNetX's built-in analytics tools, optimized for cohort construction, matching, and outcome comparison within federated EHR data. A 2-sided P-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 11,204,468 patients with obesity were identified. Of these, 39,518 patients met the criteria to be included in cohort 1 and 29,477 patients met the criteria for cohort 2 (Table 1). Patients in the sleeve gastrectomy cohort were younger, with a mean age of 43.1 years vs. 58 in the liraglutide group, and had a larger percentage of females (75.8% vs. 62.9% in the liraglutide cohort). Patients in the liraglutide cohort had a larger percentage of diabetes than those in the sleeve gastrectomy cohort (85.4% vs. 25.8%). In addition, patients in the sleeve gastrectomy group had a higher BMI (45.8 vs. 37.9). Lastly, standardized mean differences indicated imbalances across many variables prior to matching, consistent with the large sample sizes. After matching these differences were corrected for, and both groups were well matched, with 10,048 patients in each cohort, as seen in Table 1.

Outcomes

Barrett's esophagus without dysplasia was identified in 27 patients (0.3%) in the sleeve gastrectomy group and 10 patients (0.1%) in the liraglutide group, after excluding individuals with prior diagnoses (Table 2). This corresponds to a risk difference of 0.2% (95%CI 0.1-0.3%), which was

statistically significant ($z=2.791$, $P=0.005$). The RR was 2.70 (95%CI 1.31-5.56), indicating that patients who underwent sleeve gastrectomy were nearly 3 times more likely to develop Barrett's esophagus without dysplasia, compared to those treated with liraglutide. The odds ratio was elevated (OR 2.70, 95%CI 1.31-5.58), supporting increased risk following sleeve gastrectomy. Although the absolute event rate was low, these findings indicate a statistically significant increase in risk compared with liraglutide therapy.

Barrett's esophagus with dysplasia was seen in 10 patients (0.1%) in the sleeve gastrectomy cohort ($n=10,048$). No cases were observed in the liraglutide cohort ($n=10,048$) (Table 3). This corresponded to a statistically significant ($z=3.162$, $P=0.002$) risk difference of 0.1% (95%CI 0.0-0.2%). RR and OR could not be calculated for the liraglutide group, as no cases were observed. The findings indicate that there is a significantly higher risk of Barrett's esophagus with dysplasia in those who undergo sleeve gastrectomy in comparison to patients given liraglutide.

Esophageal cancer was uncommon, with 10 cases (0.1%) observed in each cohort (Table 4). There was no difference in cancer risk between the groups, with a risk difference of 0.0% (95%CI -0.1% to 0.1% ; $z=-0.001$, $P=0.999$). Both the RR and OR were 1.0 (95%CI 0.416-2.401 and 0.416-2.403, respectively), indicating no detectable association between treatment strategy and esophageal cancer during the study period.

Discussion

Our study showed that liraglutide use resulted in significantly lower rates of dysplastic and non-dysplastic Barrett's esophagus, compared to patients who underwent sleeve gastrectomy. This is at least partly due to the physiological differences in the gastrointestinal tract after surgery, such as the increased amount of reflux following sleeve gastrectomy [11,22,23]. This distinction highlights the need for careful reflux surveillance and preventive strategies in patients after sleeve gastrectomy, rather than implying that liraglutide should replace surgery as the preferred treatment [24,25].

Liraglutide's other pros include advantages in flexibility and reversibility. Liraglutide can be discontinued or readily titrated in response to side-effects [9]. Gastrointestinal anatomy is permanently changed after sleeve gastrectomy. The procedure

Table 2 Risk analysis of Barrett's esophagus without dysplasia

Group	Patients in Cohort	Patients with outcome	Risk	Risk difference	95% CI (RD)	Risk ratio	95% CI (RR)	Odds ratio	95% CI (OR)	z	P-value
Sleeve gastrectomy	10,048	27	0.003	–	–	–	–	–	–	–	–
Liraglutide	10,048	10	0.001	–	–	–	–	–	–	–	–
Comparative analysis	–	–	–	0.002	(0.001-0.003)	2.695	(1.305-5.564)	2.699	(1.306-5.579)	2.791	0.005

CI, confidence interval; RD, risk difference; RR, risk ratio; OR odds ratio

Table 3 Risk analysis of Barrett's esophagus with dysplasia

Group	Patients in cohort	Patients with outcome	Risk	Risk difference	95% CI (RD)	Risk Ratio	95% CI (RR)	Odds Ratio	95% CI (OR)	z	P-value
Sleeve gastrectomy	10,048	10	0.001	–	–	–	–	–	–	–	–
Liraglutide	10,048	0	0.000	–	–	–	–	–	–	–	–
Comparative analysis	–	–	–	0.001	(0.000-0.002)	–	(---)	–	(---)	3.162	0.002

CI, confidence interval; RD, risk difference; RR, risk ratio; OR odds ratio

Table 4 Risk analysis of esophageal cancer

Group	Patients in cohort	Patients with outcome	Risk	Risk difference	95% CI (RD)	Risk Ratio	95% CI (RR)	Odds Ratio	95% CI (OR)	z	P-value
Sleeve gastrectomy	10,048	10	0.001	–	–	–	–	–	–	–	–
Liraglutide	10,048	10	0.001	–	–	–	–	–	–	–	–
Comparative analysis	–	–	–	-0.000	(-0.001 to 0.001)	1.000	(0.416-2.401)	1.000	(0.416-2.403)	-0.001	0.999

CI, confidence interval; RD, risk difference; RR, risk ratio; OR odds ratio

can also result in complications, like strictures, hernias and anastomotic leaks, which can require further surgeries, such as conversion to Roux-en-Y gastric bypass [15-17]. Although medications have their advantages, sleeve gastrectomy tends to produce more significant and sustained weight loss, and is still favored for many patients with severe or refractory obesity [5-7,26-29].

While the difference in the incidence of Barrett's esophagus was significant statistically, absolute risk differences were low. The statistical significance appears to be driven mainly by the large sample size, rather than by a clinically meaningful effect. This distinction is clinically important, and suggests that these findings should inform risk stratification and counseling rather than dictate treatment selection.

No difference in esophageal cancer incidence was observed between cohorts; however, this finding should be interpreted judiciously. The latency between Barrett's esophagus and malignant transformation often spans decades [24,25]; thus, longer-term studies are warranted.

Our study is clinically relevant, as it stresses individualized obesity management as an important concept. Liraglutide as a treatment option is not invasive and can be reversed. This option can be appealing for patients with preexisting reflux, those with a higher surgical risk, or individuals for whom temporary therapy is desirable, including patients of reproductive age or transplant candidates [18-21]. It is important that patients undergoing sleeve gastrectomy be adequately counseled regarding the postoperative reflux risk and the potential need for long-term acid suppression and endoscopic surveillance [30-32].

This study has several limitations inherent to TriNetX retrospective database analyses. Medication adherence and symptom severity could not be directly assessed. We addressed this limitation by including patients who had

liraglutide listed as an active medication at least 3 years after starting the medicine. Since the progression of disease in Barrett's esophagus and esophageal cancer is slow, we selected liraglutide because it has the longest FDA approval history for obesity [9,33]. Additionally, we required a follow-up period of at least 6 years after the medication was initially prescribed. Finally, the ICD-10-CM coding system does not differentiate esophageal cancer by histological subtype, and our dataset used code C15.9 (malignant neoplasm of esophagus, unspecified). However, esophageal adenocarcinomas developing from Barrett's esophagus make up most of the esophageal cancers in the United States. It should be noted that the sample sizes were not sufficient to allow for stratification based on the grade of dysplasia.

In conclusion, different effects on reflux physiology, rather than obesity control, are likely to explain why liraglutide was associated with a lower incidence of Barrett's esophagus than was sleeve gastrectomy. Our study emphasizes reflux management and surveillance after sleeve gastrectomy, rather than supporting liraglutide as a replacement for surgery. Future studies with extended follow up are warranted to evaluate the long-term cancer risk, metabolic durability, and cost-effectiveness across pharmacologic and surgical obesity treatments.

AI use disclosure

Generative artificial intelligence tools were used only for language refinement and stylistic editing. The study conception, design, data analysis, interpretation and clinical conclusions are those of the authors.

Summary Box

What is already known:

- Obesity is a well-established risk factor for gastroesophageal reflux disease (GERD), Barrett's esophagus, and esophageal cancer
- Sleeve gastrectomy, while effective for weight loss, is associated with high rates of postoperative GERD and Barrett's esophagus
- Liraglutide, a short-acting glucagon-like peptide-1 receptor agonist, has been linked to GERD in some observational studies
- The long-term impact of liraglutide vs. sleeve gastrectomy on esophageal complications such as Barrett's esophagus and esophageal cancer remains unclear

What the new findings are:

- Sleeve gastrectomy is associated with a significantly higher risk of developing Barrett's esophagus (with and without dysplasia) compared to liraglutide
- There was no significant difference in esophageal cancer incidence between the 2 treatment groups
- Liraglutide may be a suitable option for patients at higher risk of reflux-related complications, particularly younger or reproductive-age individuals, while not replacing surgery as the preferred intervention for durable weight loss

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