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Original Contribution

Relationship between perioperative semaglutide use and residual gastric content: A retrospective analysis of patients undergoing elective upper endoscopy

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HIGHLIGHTS

- Semaglutide, a GLP-1 agonist, has been associated with delayed gastric emptying.
- 5.1% of patients not using semaglutide had increased residual gastric content (RGC).
- 24.2% of patients taking semaglutide perioperatively had increased RGC ($p < 0.001$).
- Presence of pre-endoscopy digestive symptoms was also associated with increased RGC.
- Interval of preoperative semaglutide cessation was not predictive of increased RGC.

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ABSTRACT

Study objective: Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist used for management of type 2 diabetes and/or obesity. To test the hypothesis that perioperative semaglutide use is associated with delayed gastric emptying and increased residual gastric content (RGC) despite adequate preoperative fasting, we compared the RGC of patients who had and had not taken semaglutide prior to elective esophagogastroduodenoscopy. The primary outcome was the presence of increased RGC.
Design: Single-center retrospective electronic chart review.
Setting: Tertiary hospital.
Patients: Patients undergoing esophagogastroduodenoscopy under deep sedation/general anesthesia between July/2021–March/2022.
Interventions: Patients were divided into two (SG = semaglutide, NSG = non-semaglutide) groups, according to whether they had received semaglutide within 30 days prior to the esophagogastroduodenoscopy.
Measurements: Increased RGC was defined as any amount of solid content, or > 0.8 mL/Kg (measured from the aspiration/suction canister) of fluid content.
Main results: Of the 886 esophagogastroduodenoscopies performed, 404 (33 in the SG and 371 in the NSG) were included in the final analysis. Increased RGC was observed in 27 (6.7%) patients, being 8 (24.2%) in the SG and 19 (5.1%) in the NSG ($p < 0.001$). Semaglutide use [5.15 (95%CI 1.92–12.92)] and the presence of preoperative digestive symptoms (nausea/vomiting, dyspepsia, abdominal distension) [3.56 (95%CI 2.2–5.78)] were

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associated with increased RGC in the propensity weighted analysis. Conversely, a protective [0.25 (95%CI 0.16–0.39)] effect against increased RGC was observed in patients undergoing esophagogastroduodenoscopy combined with colonoscopy. In the SG, the mean time of preoperative semaglutide interruption in patients with and without increased RGC was 10.5 ± 5.5 and 10.2 ± 5.6 days, respectively ($p = 0.54$). There was no relationship between semaglutide use and the amount/volume of RGC found on esophagogastroduodenoscopy ($p = 0.99$). Only one case (in the SG) of pulmonary aspiration was reported.

Conclusions: Semaglutide was associated with increased RGC in patients undergoing elective esophagogastroduodenoscopy. Digestive symptoms prior to esophagogastroduodenoscopy were also predictive of increased RGC.

1. Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists increase insulin production, reduce glucagon production, induce satiety, and may delay gastric emptying. They became available in 2005 for managing type 2 diabetes and obesity. Measurement of (delayed) gastric emptying has been suggested as a biomarker of GLP-1 agonists responsiveness and for determination of suitability for prolonged treatment [1]. Semaglutide, a GLP-1 agonist with a half-life of ~7 days, has gained popularity due to its convenient (once-weekly) dosage resulting in weight loss and improved cardiometabolic profile even in non-diabetic patients [2,3].

In the metabolic literature, a commonly used indirect method of measuring gastric emptying is through determining serum paracetamol concentration after paracetamol ingestion with a meal. Paracetamol is not absorbed in the stomach but is absorbed almost immediately upon entering the duodenum. Assuming that the passage time of paracetamol through the stomach is identical to that of the meal, one can estimate gastric emptying based on the time course of the plasma paracetamol concentration. Delayed gastric emptying secondary to GLP-1 agonists use has been found in some [4–6], but not all [7], studies in the non-preoperative fasted setting based on this method.

Delayed gastric emptying has important anesthetic implications. Given the lack of reports examining the correlation between perioperative GLP-1 agonists use and residual gastric content (RGC) in the anesthesiology literature, we aimed to investigate the relationship between perioperative semaglutide use and RGC in patients undergoing elective upper endoscopy (UE) under deep sedation or general anesthesia. During UE, the entire stomach contents are meticulously emptied under direct vision and represent a direct (and presumably accurate) measurement of gastric contents. We therefore decided to study UE patients to test the hypothesis that semaglutide is associated with increased RGC despite adequate preoperative fasting.

2. Materials and methods

In this retrospective observational study, we reviewed electronic medical records of all patients undergoing elective UE under deep sedation and/or general anesthesia between July/2021–March/2022 at Vila Nova Star Hospital. All included patients complied with our institutional ($\geq$ 2 h for clear fluids, and $\geq$ 8 h for solids and fluids with residue) fasting guidelines. All patients $\geq$ 18 years-old presenting for elective diagnostic UE were eligible. Exclusion criteria were: gastric outlet obstruction, gastric volvulus, frank/active esophageal/gastric/duodenal bleeding, American Society of Anesthesiologists Physical Status (ASA-PS) $\geq$ IV, recent ($\leq$ 2 months) abdominal surgery, emergency endoscopic procedures, UE combined with other/surgical procedures, chronic renal and/or liver disease, achalasia, Zenker's diverticulum, linitis plastica, multiple myeloma, systemic collagenosis, amyloidosis, pregnancy, chronic opioid use, drug addiction, use of vasoactive agents, patients admitted to the intensive care unit, preoperative use/ingestion of medication known to affect gastric emptying (e.g., tricyclic antidepressants, opioids, pro-kinetics, histamine H2-receptor antagonists) other than semaglutide, and incomplete medical records. Patients using GLP-1 agonists other than semaglutide were also excluded. Primary outcome was the presence of increased RGC defined as any amount of solid content from the esophagus to the pylorus, or > 0.8 mL/Kg of fluid content as measured from the aspiration/suction canister. Notably, we assumed that > 0.8 mL/Kg of fluid content would characterize a higher risk for broncho-aspiration based on previous work by Bouvet et al. [8]. Upon esophageal intubation, the endoscopist performed a complete gastric inspection/examination and aspirated all gastric contents into a graduated canister via the endoscope. All UE reports and images were digitally recorded and stored in the institutional database. The RGC volume was routinely visually (small, medium, or large) [9,10] estimated by the endoscopist (Fig. 1). Secondary outcome was the incidence of perioperative broncho-aspiration. The following demographic and past medical data were recorded: age, height, weight, sex, ASA-PS, previous surgical procedure(s), preoperative fasting time (for fluids and solids), presence and type (diet-controlled, type 1, type 2) of diabetes and other comorbidities including psychiatric illness(es) requiring pharmacologic/medical intervention. Additionally, the presence of ongoing digestive symptoms (nausea/vomiting, dyspepsia, and/or abdominal distension) on the day of/immediately pre-UE was assessed through a standardized questionnaire. Notably, the perioperative use of GLP-1 agonists has been mandatorily recorded during pre-anesthetic evaluations at our institution since July/2021 when a quality improvement policy requiring cross reference of at least two sources of medication reconciliation (e.g., patient/family member reports, pharmacy list, available medical record/chart) was implemented. In total, 886 UEs were performed, of which 404 were included in the final analysis (Fig. 2). Patients were grouped according to whether they had received preoperative semaglutide subcutaneously once/week (semaglutide group, or SG) and patients not exposed to semaglutide (non-semaglutide group, or NSG) within 30 days prior to the UE. Indications for semaglutide in all included patients were management of diabetes and/or promotion of weight loss. Notably, when the primary indication was diabetes mellitus and semaglutide was discontinued prior to the UE, glycemic control was managed with diet control and/or insulin (using a sliding scale) at the discretion of the attending endoscopist. The last day of semaglutide administration pre-UE was recorded. Since the (weekly) dosage was unavailable, it was not analyzed. Lastly, while patients scheduled for elective UE at our institution are routinely instructed to discontinue their semaglutide 10–14 days prior to the procedure, some patients (and for a variety of reasons, such as short notice to fill in for an unforeseen UE cancelation) did not follow this instruction.

Premedication was not routinely administered. The sedation/anesthetic procedure was at the discretion of the anesthesiologist. Intraoperative monitoring consisted of sphygmomanometry, electrocardiography, pulse oximetry, and capnography.

This investigation was approved by the Institutional Research Ethics Board (IREB) (protocol 5.414.154, CAAE 58725222.3.0000.0087) who waived informed consent. STROBE guidelines were followed, and this study complied with Resolution 466/2012 of the Brazilian National Health Council.

2.1. Statistical analysis

The sample size was based on the available data, i.e., all patients who underwent UE between July/2021–March/2022. No statistical power calculation was performed before the study.

The normality of the data distribution was assessed using the normal quantile–quantile (QQ) plot. Pearson Chi-squared test was employed for categorical variables, and partitioning Chi-square when $p < 0.05$. The Mann-Whitney *U* test was used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. The inverse of the propensity scores (PS) was used to weight the patient cohort for the treatment group (SG) and 1/(1-PS) for the control group (NSG), thus the term Inverse Probability Treatment Weighting (IPTW). In addition to covariate adjusted Poisson regression model (with robust variance), we performed a propensity weighted analysis using IPTW to estimate the prevalence ratios (PR) with associated 95% confidence intervals (95%CI). The propensity score was constructed with a wide array of independent variables: age, sex, body mass index (BMI), diabetes mellitus, hypertension, psychiatric illness, ASA-PS classification, fasting duration for clear fluids, fasting duration for solids and/or fluids with residue, proton-pump inhibitors, previous fundoplicature for gastroesophageal reflux disease, previous other gastric surgeries, and colonoscopy combined with UE. Absolute standardized differences were calculated to assess the presence of residual differences in measured covariates following cohort weighting [11]. When this standardized difference was < 0.1, we considered the groups to be balanced on the covariate [12]. In addition to numeric comparisons of balance, QQ plots were used for this purpose. We evaluated the overlapping assumption of propensity scores using density and histogram plots.

STATA® (version 17.0, College Station, TX) was used for all analyses. QQ plots were performed using R software version 3.4.4 (R Foundation for Statistical Computing, Austria). The research data related to this submission has been published in Mendeley Data (https://data.mendeley.com/drafts/78ghfpj225; doi: 10.17632/78ghfpj225.1). The files associated with this dataset are licensed under an attribution non-commercial 3.0 Unported license (CC BY NC 3.0).

3. Results

This cohort included 404 patients (33 in the SG and 371 in the NSG), of whom 48.5% were female. The median age was 50 (39–64) years. The primary indication for semaglutide use was predominantly promotion of weight loss (87.8%), followed by management of diabetes mellitus (12.2%). Obesity (BMI > 30 kg.m^{-2}) was observed in 19.9% of included patients. Table 1 shows the participants' demographic and clinical characteristics. Increased RGC was observed in 27 (6.7%) patients, being 8 (24.2%) in the SG and 19 (5.1%) in the NSG ($p < 0.001$). Solid content was observed in 85.2% of patients with increased RGC. Supplementary Table 1 shows the participants' demographic and clinical characteristics according to residual gastric solid content. Fasting intervals for clear fluids and solids were 9.3 (5.0–12.8) and 14.5 (12.2–28.7) hours, respectively. In total, 38 (9.4%) patients were treated for diabetes, being 4 (10.6%) in the SG and 34 (89.4%) in the NSG. The unadjusted analysis showed that semaglutide use [PR = 4.73 (95%CI 2.07–10.81)] and the presence of ongoing digestive symptoms [PR = 6.1 (95%CI 2.67–13.98)] were significantly associated with increased RGC. Conversely, when UE was combined with colonoscopy, a protective [PR = 0.13 (95%CI 0.15–0.78)] effect against increased RGC was observed (Table 1). Fasting intervals for clear fluids and solids did not differ in relation to the presence/absence of increased RGC (Suppl. Fig. 1). Supplementary Table 2 shows the relationship between the presence of clinical conditions and/or ongoing upper GI symptoms and the need for elective UE according to the presence/absence of increased RGC.

Since balancing the distribution of relevant variables between non-users and users of semaglutide is the main reason for propensity score estimation, covariate balancing test is presented in Suppl. Table 3 and clinical characteristics between semaglutide users and non-users in Suppl. Fig. 2. The standardized differences of the covariates before and after IPTW show that the heterogeneous cohorts became homogeneous after propensity score estimation. The QQ plot shows that the majority of points remain near the center line for the matched QQ plots (Suppl. Fig. 3). This pattern indicates that patients at each quantile in the distribution had similar scores on the covariates.

In the weighted analysis, semaglutide use [PR = 5.15 (95%CI 1.92–12.92)] and the presence of ongoing digestive symptoms prior to the UE [PR = 3.56 (95%CI (2.2–5.78)] remained significantly associated with increased RGC, while UE combined with colonoscopy had a protective effect [PR = 0.25 (95%CI (0.16–0.39)] (Table 2). In the weighted analysis including a composite variable 'semaglutide use *versus* presence of ongoing digestive symptoms', semaglutide use and the presence of digestive symptoms pre-UE showed a higher prevalence ratio [PR = 16.5 (95%CI (9.0–34.91)] compared to semaglutide use in the absence of ongoing digestive symptoms [PR = 9.68 (95%CI (5.6–17.66)] (Table 2).

The time intervals of semaglutide interruption in patients with and without increased RGC were 10 (6–15) and 11 (7.75–12.5) days, respectively ($p = 0.67$) (Suppl. Fig. 4). There was no variable associated with increased RGC in semaglutide users (Suppl. Table 4). Among the 27 patients who were found to have increased RGC, the RGC was visually estimated as small, moderate, and large, in 7 (25.9%), 7 (25.9%), and 13 (48.1%) patients, respectively. There was no relationship between semaglutide use and the amount of RGC found on UE ($p = 0.99$) (Suppl. Table 5).

Ongoing digestive symptoms prior to UE were reported by 26 (6.4%) patients. Suppl. Table 6 shows the univariate analysis including potential factors associated with ongoing digestive symptoms. In the adjusted analysis, age [PR = 0.93 (95%CI 0.83–0.99)] and semaglutide use [PR = 5.48 (95%CI 2.31–12.98)] were independently associated with ongoing digestive symptoms (Suppl. Table 7). The average age was lower among symptomatic patients ($p < 0.001$) (Suppl. Fig. 5).

In total, 392 (97.0%) patients underwent UE under deep sedation, and 12 (3.0%) received a general anesthetic. Only one (0.24%) case (under deep sedation) of broncho-aspiration was reported. This was a 63-year-old man, with BMI = 37.7 kg.m^{-2} and history of hypertension, previous gastric bypass, and preoperative use of semaglutide (last dose 11 days pre-UE), and whose fasting interval (12.4 h for both clear fluids

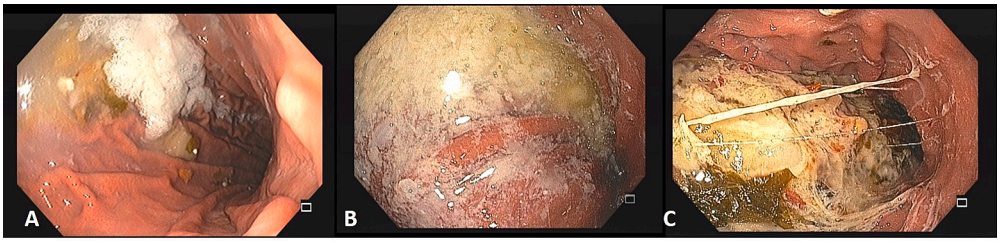

Fig. 1. Upper endoscopy images showing amount of residual gastric content as visually estimated by the attending endoscopist: **(A)** Small, **(B)** Medium, **(C)** Large. Notably, all images were from patients using perioperative semaglutide.

and solids) was in compliance with our institutional guidelines. This patient denied ongoing digestive symptoms pre-UE.

4. Discussion

Preoperative fasting has long been adopted to decrease RGC and mitigate aspiration risk prior to induction of anesthesia. Certain medical conditions, however, are associated with delayed gastric emptying and increased gastric content despite adequate (or even prolonged) fasting intervals [13,14].

GLP-1 agonists have been associated with delayed gastric emptying [4–6], but to date, reports examining the relationship between perioperative semaglutide use and increased RGC (and broncho-aspiration) are lacking. Hence, several questions remain unanswered: (i) is perioperative semaglutide use associated with higher gastric contents? (ii) given its ~1-week half-life, how long should semaglutide be interrupted preoperatively? (iii) what is the ideal/safe preoperative fasting interval (if different than recommended by current guidelines) for patients using semaglutide undergoing elective surgical/anesthetic procedures? We aimed to answer the first of these questions. Notably, designing a clinical trial to investigate the relationship between perioperative semaglutide use and broncho-aspiration would present several ethical and methodological limitations. Indeed, deliberately exposing patients to the potential risk of broncho-aspiration would be ethically unjustifiable. Additionally, the low incidence of pulmonary aspiration (one in every 2000–3000 anesthetic procedures) [14] would require a very large sample size. In this context, a retrospective analysis using RGC as a surrogate to identify at-risk patients for broncho-aspiration seems appealing, at the very least for hypothesis generation. Furthermore, patients undergoing elective UE possibly represent the ideal population given that they (i) are appropriately fasted and routinely have their RCG (ii) visually estimated and (iii) quantitatively measured as part of the procedure. Notably, scintigraphy-based studies have demonstrated a strong correlation between the presence (and quantity) of RGC and delayed gastric emptying [9,15]. Moreover, increased RGC has been used as a surrogate for gastroparesis in previous reports [16].

In a large retrospective cohort of 85,116 patients undergoing esophagogastroduodenoscopy, Bi et al. [15] reported a 3% incidence of retained gastric food. Conversely, the incidence of residual gastric solid content in our cohort was significantly higher (5.7%), even after excluding patients using semaglutide (4.6%). Such considerable differences are likely multifactorial. A selection bias might have been present given that our institution manages primarily complex oncological patients. Nevertheless, our findings (and those from Bi et al. [15]) underscore increased RGC as a somewhat common entity affecting several patients perioperatively (despite “adequate” preoperative fasting) and highlight the need for further investigations particularly focused on associated risk factors and the incidence of perioperative broncho-aspiration.

According to our findings, perioperative use of semaglutide was associated with a prevalence ratio for increased RGC of 5.15 (95%CI 1.92–12.92) in the weighted analysis. Interestingly, perioperative use of GLP-1 agonists was not associated with retained gastric food among Bi et al.’s large cohort of patients undergoing esophagogastroduodenoscopy [15]. Notably, however, their study was underpowered for such outcome since only 6 (out of 85,116 patients) had reportedly been using GLP-1 agonists perioperatively [15] (versus 33 out of 404 patients in our cohort). Nevertheless, the odds of retained gastric food in Bi et al.’s [15] cohort were increased in patients with type 1 diabetes (OR = 1.7, $p \leq 0.001$), type 2 diabetes (OR = 1.4, $p \leq 0.001$), amyloidosis (OR = 1.7, $p \leq 0.001$), structural foregut abnormalities (OR = 2.6, $p \leq 0.001$), and gastroparesis (OR = 4.8, $p \leq 0.001$), of which only the latter was comparable to (or, as high as) semaglutide use (PR = 5.15, 95%CI 1.92–12.92) found in our cohort, which corroborates our hypothesis that semaglutide is associated with delayed gastric emptying/gastroparesis and increased RGC.

Current guidelines recommend preoperative fasting of 2 h for clears fluids and 6–8 h for solids and fluids with residue [17,18]. In fact, our institutional fasting guidelines for patients scheduled for UE assume a minimum of 4 h for clear fluids and 12 h for solids and fluids with

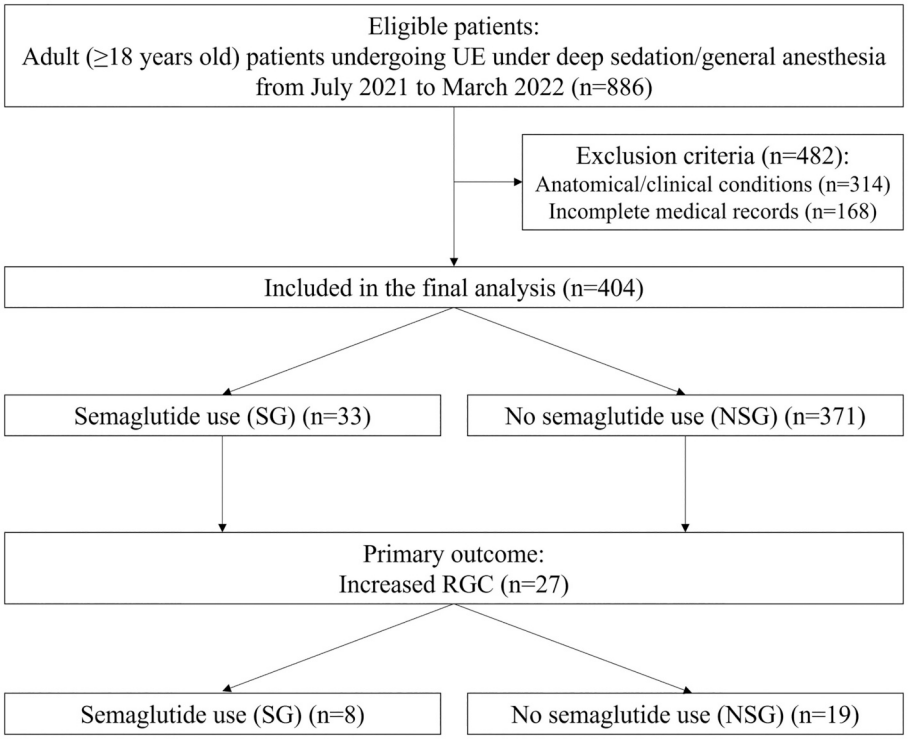

Fig. 2. Study flow chart in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (http://www.strobestatement.org). UE = upper endoscopy; RGC = residual gastric content.

Table 1
Demographic and clinical characteristics of 404 patients undergoing elective upper endoscopy according to the presence/absence of increased residual gastric content (Univariate analysis using the Poisson regression model).

Variables		Increased residual gastric content†		Unadjusted PR (95% CI)	*P*-value
	Total (n = 404)	No (n = 377)	Yes (n = 27)		
Age (years)[1]	50.8 (39–64)	51.3 (40–64)	45.0 (33.5–59.5)	0.97 (0.95–1.00)	0.053
Sex[2]					0.464
Female	48.5 (196)	48.0 (181)	55.6 (15)	1.00	
Male	51.5 (208)	52.0 (196)	44.4 (12)	0.75 (0.35–1.61)	0.464
BMI[1] (kg.m^{-2})	26.2 (22.98–28.73)	26.1 (23–28.7)	27.0 (25.1–32.8)	1.03 (0.96–1.10)	0.974
Fasting duration for clear liquids[1] (hours)	9.3 (5–12.81)	9.2 (4.95–12.8)	10.8 (7.79–12.5)	1.06 (0.99–1.14)	0.084
Fasting duration for solids[1] (hours)	14.5 (12.19–28.73)	14.0 (12.3–16.3)	13.9 (11.8–14.4)	0.95 (0.85–1.07)	0.457
ASA-PS classification[2]					
I	19.3 (78)	19.6 (74)	14.8 (4)	1.00	
II	71.0 (287)	70.8 (267)	74.1 (20)	1.35 (0.46–3.97)	0.575
III	9.7 (39)	9.5 (36)	11.1 (3)	1.50 (0.33–6.70)	0.595
Hypertension[2]	26.6 (103)	26.1 (98)	18.5 (5)	0.66 (0.25–1.74)	0.405
Diabetes Mellitus[2]	9.4 (38)	9.5 (36)	7.4 (2)	0.77 (0.18–3.25)	0.722
Psychiatric illness[2]	29.2 (118)	28.1 (106)	44.4 (12)	1.93 (0.90–4.14)	0.087
Treated hypothyroidism[2]	18.3 (74)	18.3 (69)	18.5 (5)	1.01 (0.38–2.67)	0.978
Dyslipidemia[2]	22.3 (90)	22.8 (86)	14.8 (4)	0.60 (0.20–1.75)	0.356
Semaglutide use[2#]	8.1 (33)	6.6 (25)	29.6 (8)	4.73 (2.07–10.81)	<0.001
Proton-pump inhibitors[2]	13.5 (55)	13.1 (49)	22.22 (6)	1.5 (0.54–4.14)	0.42
Previous fundoplicature for GERD[2]	6.9 (28)	6.6 (25)	11.1 (3)	1.67 (0.50–5.57)	0.397
Previous other gastric surgeries[2]	11.4 (46)	10.6 (40)	22.2 (6)	2.22 (0.89–5.50)	0.084
Colonoscopy combined with upper endoscopy[2]	55.0 (222)	56.8 (214)	29.6 (8)	0.13 (0.15–0.78)	0.011
Digestive symptoms[2#]	6.4 (26)	4.8 (18)	29.6 (8)	6.12 (2.67–13.98)	<0.001
Semaglutide versus Digestive symptoms[2##]					<0.001
No Semaglutide use and no digestive symptoms	87.6 (354)	95.8 (339)	4.2 (15)	1.00	
Semaglutide use and digestive symptoms	2.2 (9)	55.6 (5)	44.4 (4)	10.49 (3.48–31.60)	<0.001
Semaglutide use and no digestive symptoms	5.9 (24)	83.3 (20)	16.7 (4)	3.93 (1.30–11.85)	0.014
No Semaglutide use and digestive symptoms	4.2 (17)	76.5 (13)	23.5 (4)	5.55 (1.84–16.73)	0.002

Abbreviations: Body mass index (BMI) (kg.m^{-2}); Gastroesophageal reflux disease (GERD); The American Society of Anesthesiologists Physical Status (ASA-PS) classification; Confidence Interval (CI); Prevalence ratio (PR). †Increased residual gastric content was defined as any amount of solid content from the pharynx to the pylorus, or > 0.8 mL/Kg of fluid content as measured from the aspiration/suction canister. [1] Values expressed as median (percentile 25–75%); [2] Values expressed as % (n). *P*-values are based on regression analysis.

Table 2
Summary of propensity weighted analysis.

	Propensity weighted analysis (A)		
	Estimate (PR)	95% CI	P-value
Semaglutide use	5.15	1.92–12.92	<0.001
Digestive symptoms	3.56	2.2–5.78	<0.001
Colonoscopy combined with upper endoscopy	0.25	0.16–0.39	<0.001
	Propensity weighted analysis (B)		
	Estimate (PR)	95% CI	P-value
Semaglutide use and digestive symptoms	16.5	9.08–34.91	<0.001
Semaglutide use and no digestive symptoms	9.68	5.6–17.66	<0.001
No Semaglutide use and digestive symptoms	4.94	1.32–15.77	0.0098
Colonoscopy combined with upper endoscopy	0.26	0.16–0.39	<0.001

Estimates correspond to prevalence ratio (PR). CI = confidence interval. (A) Weighted analysis including semaglutide use and presence of digestive symptoms prior to upper endoscopy, separately; (B) Weighted analysis with a combined variable semaglutide versus presence of digestive symptoms prior to endoscopy. Robust covariance estimates were used for all propensity weighted analyses.

residue. These rather (over-)conservative recommendations have been agreed upon by our local attending endoscopists and anesthesiologists and aim to minimize gastric residue that may not only hinder the examination, but also increase the risk of aspiration in a patient population that, in its great majority (97%), will undergo the UE under deep sedation without endotracheal intubation. This is reflected by the average fasting intervals (9.3 h for clear fluids and 14.5 h for solids) observed in our cohort (Table 1), and is in line with previous reports that found a median 13.9-h fasting interval prior to UE [19]. Importantly, current perioperative fasting recommendations [17,18] are based on data derived from healthy individuals, since "at-risk" patients (e.g., diabetes, previous foregut surgery, elderly and/or obese patients) have been deliberately excluded from prospective studies [17,18,20]. Additionally, meal-related (last meal's volume, particle size, caloric density, fat and fiber percentage) and gastric (pH, antral motility, gastric accommodation) factors that directly affect gastric emptying [21] have rarely been considered in these investigations [17,18]. Importantly, given the recent introduction of GLP-1 agonists into clinical practice, traditional fasting guidelines [17,18] have largely overlooked their (well-documented) delayed gastric emptying effect [4,6,22]. In fact, even guidelines assessing the role of endoscopy in patients with known gastroparesis have apparently failed to address the ideal pre-procedure fasting intervals [23]. Also noteworthy is the fact that studies supporting current fasting guidelines are based primarily on clinical (bronchoaspiration) outcomes rather than direct endoscopic visualization/quantification of gastric contents. Hence, the true validity (and perhaps, most importantly, generalizability) of such recommendations for ensuring an "empty" stomach preoperatively remains debatable, especially when accounting for (highly heterogeneous) "at-risk" populations. Further investigations (ideally based on direct quantification of RGC) are therefore warranted to better inform perioperative guidelines regarding ideal fasting intervals. Future studies should be tailored to different patient populations considering both patient and procedural underlying factors. For instance, given the high prevalence of increased RGC identified in the present investigation (as well as in previous reports) [15] despite the observed longer-than-recommended pre-procedure fasting intervals, one may argue that patients undergoing UE should be routinely considered for pre-endoscopy fasting intervals that

are significantly longer than those recommended by traditional guidelines to ensure optimal technical conditions and patient safety.

When UE was combined with colonoscopy, a protective [PR = 0.25 (95%CI (0.16–0.39)] effect was observed against increased RGC compared to UE alone. Given that food characteristics interfere with gastric emptying [21] (with different fasting intervals recommended for different types of food) [17], the residue-free diet (i.e., no seed-containing food 5 days prior to the exam, fiber-free diet 24 h prior to the exam, and liquid diet on the evening pre-exam) routinely prescribed to our patients for bowel preparation prior to colonoscopy might have played a role. Notably, there are marked differences between the solutions used locally (mannitol) and elsewhere (polyethylene glycol) [24–26] for bowel preparation with regards to osmolarity, total volume administered, and time recommended between the last dose and the beginning of the procedure. Nevertheless, a simple intervention to further reduce/eliminate RGC prior to UE would be a liquid diet on the day prior to the exam, although further studies are needed to confirm its benefits/effects.

There is currently no standardized method to quantifying the RGC volume identified by endoscopy. At our institution, as described in previous studies [9,10,15], endoscopists visually estimate this volume as small, medium or large (Fig. 1). Given the direct correlation between RGC volume and the risk of broncho-aspiration [13], one can assume that patients presenting with medium/large RGC (reported at 73–84% of patients undergoing UE) [9,15] are at greater risk of aspiration. In our sample, medium/large RGC volumes were found in 74% of patients and there was no relationship between perioperative semaglutide use and RGC volume ($p = 0.99$).

Gastrointestinal symptoms are common among patients using semaglutide with an incidence of nausea, vomiting and diarrhea reported at 11.4–20%, 4–11.5%, and 4.5–11.3%, respectively [27–29]. In a trial evaluating semaglutide use and cardiovascular outcomes in patients with type 2 diabetes, nausea, vomiting and diarrhea were the most frequent side effects (51%) and the main cause for semaglutide discontinuation (13%) [30]. In our cohort, ongoing digestive symptoms were positively [PR = 3.56 (95%CI (2.2–5.78)] correlated with increased RGC. Conversely, nearly 25% of patients with chronic nausea and vomiting present with normal gastric emptying as evidenced by scintigraphy [31], and not every patient with increased RGC has evidence of gastroparesis [15]. Nevertheless, our weighted analysis showed a remarkably higher risk of increased RGC in patients presenting with ongoing digestive symptoms concurrent with perioperative semaglutide use [PR = 16.5 (95%CI (9.08–34.91)] (Table 2). One, therefore, may argue that inquiring about ongoing digestive symptoms during the pre-anesthetic assessment is not only simple and cost-effective, but also may improve anesthesiologists' ability to identify patients at a higher risk of increased RGC (and broncho-aspiration), especially among those in concomitant perioperative semaglutide use. Lastly, the absence of ongoing digestive symptoms in patients on regular use of semaglutide was associated with a lower, albeit still elevated [PR = 9.68 (95%CI 5.6–17.66)], risk of increased RCG.

A GLP-1 agonist infusion has been shown to inhibit gastric emptying in type 2 diabetic patients [32]. Recent studies have suggested that this inhibitory effect depends on the duration of medication exposure, with evidence of delayed postprandial early-emptying after 12 weeks of treatment [33], which tends to subside/resolve after 20 weeks [7]. Accordingly, common side effects (e.g., nausea/vomiting) that can be potentially attributed to delayed gastric emptying tend to peak at around 12 weeks of treatment [34], and subsequently subside, with patients reporting mild to moderate gastrointestinal symptoms for up to 30 weeks of semaglutide use [30]. Some authors have observed a reduction in delayed gastric emptying over time which has been attributed to tachyphylaxis [6,7,35,36] (which is apparently more common with long-acting GLP-1 agonists, such as semaglutide) [6]. It has been postulated that such tachyphylaxis derives primarily from altered vagal nerve function rather than GLP-1 receptor downregulation and/or desensitization [6]. Nevertheless, while there appears to be a positive correlation between digestive symptoms and delayed gastric emptying in patients using GLP-1 agonists, the origin of ongoing nausea and/or vomiting is likely multifactorial as nausea often occurs even during fasting intervals [37] and regardless of the postprandial gastric emptying velocity [32]. Accordingly, a central nervous system (i.e., reduced brain penetrance) effect has been recently suggested in an animal model, resulting in lower incidence of vomiting, despite retaining glucose control effects [37]. All in all, even though the precise mechanism(s) resulting in digestive symptoms in patients on GLP-1 agonists remain a subject of debate, caution is advised, particularly during the initial 8–12 weeks of treatment, which correspond to the highest incidence of nausea [34] and, therefore, may be a critical interval for the risk of perioperative broncho-aspiration.

GLP-1 agonists-induced delayed gastric emptying is thought to be dose-dependent [22]. Indeed, higher (1.0 mg) doses of semaglutide were associated with higher incidence of nausea (21.9% vs 17.3%) and vomiting (10.5% vs 14.8%), and higher likelihood (4.2% vs. 2.2%) of unanticipated medication discontinuation compared to lower (0.5 mg) doses [30].

Only one case of pulmonary aspiration was reported in our cohort. This was a 63 years-old hypertensive man, with previous history of gastric bypass and using semaglutide (last dose 11 days pre-UE) whose fasting interval (12.4 h) was in compliance with our local guidelines. Notably, despite pulmonary aspiration being a rare (one in every 2000–3000 procedures under anesthesia) [14] event, when a disproportionately large amount of gastric residue is identified during UE, it is our routine practice to either immediately interrupt the endoscopic exam, or to proceed with orotracheal intubation to protect the patient against broncho-aspiration.

This study contains limitations. First, given its retrospective design, many (482 or 54.4%) medical records were excluded (Fig. 2). Secondly, while name (semaglutide, liraglulide, and dalaglutide) and date of GLP-1 agonists last dose are routinely included as part of our institutional pre-anesthetic assessment, several charts lacked the specific dosage/posology as well as start date of GLP-1 agonists therapy. Posology and time interval since therapy initiation may directly impact the occurrence/degree/severity of delayed gastric emptying [6,7,22,35,36] and their analysis could therefore provide relevant and valuable data. Thirdly, our rather small sample (only 33 patients using semaglutide) was not sufficiently powered to determine the ideal/safe time interval (if there is one) of preoperative semaglutide interruption prior to elective surgical/anesthetic procedures. Fourthly, the fasting time in our cohort (Table 1) was substantially longer than what is currently recommended [17,18], which may have contributed to a lower incidence of increased RGC. Fifthly, the retrospective nature of the study and the fact that the measurement of the gastric content was performed by different endoscopists and in a qualitive scale could be considered a potential bias. Finally, our cohort included predominantly non-diabetic patients using semaglutide for weight loss.

In conclusion, perioperative semaglutide use was associated with increased RGC in patients undergoing elective UE. The presence of ongoing digestive symptoms prior to endoscopy was also a predictor of increased RGC. Further studies are warranted to better understand the impact of semaglutide's dosage and/or treatment duration on RGC and, most importantly, to determine the ideal preoperative fasting interval, and the true risk-benefit ratio of therapy (dis-)continuation perioperatively. For poorly controlled diabetic patients scheduled to undergo elective surgical procedures, the benefits of bridging semaglutide with shorter-acting anti-diabetic agents, although clinically and pharmacologically plausible, remain speculative at this time.

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Ethics statement

This investigation was approved by the Hospital São Luiz & Rede D'or and Affiliated Teaching Hospitals Research Ethics Committee (Protocol # 5.414.154; CAAE: 58725222.3.0000.0087). Patient consent for publication not required.

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Declaration of Competing Interest

None.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2023.111091.

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