Journal Pre-proof

Effects of Glucagon-Like Peptide-1 Receptor Agonists on Upper Gastrointestinal Endoscopy: A Meta-Analysis

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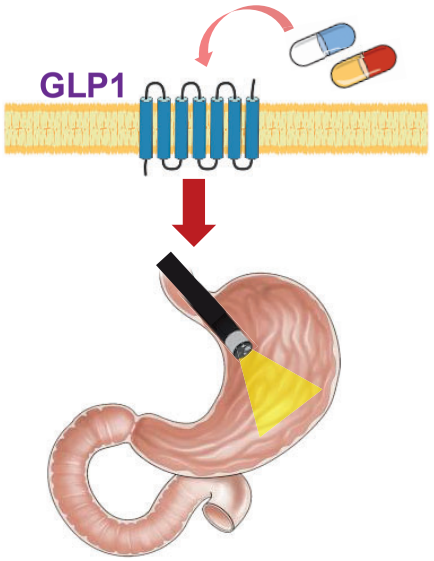
Effects of Glucagon-Like Peptide-1 receptor agonists on upper gastrointestinal endoscopy: A meta-analysis

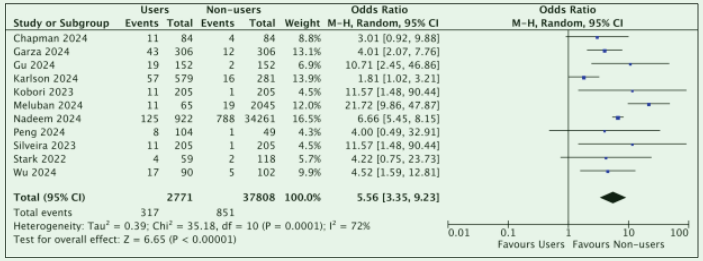


177 studies identified (2015-2023)

13 studies included

84,065 patients

Pooled rates of retained gastric content higher in GLP-1RA users (OR 5.56)



Study or Subgroup	Users Events	Users Total	Non-users Events	Non-users Total	Weight	Odds Ratio M-H, Random, 95% CI
Chapman 2024	11	84	4	84	8.8%	3.01 [0.92, 9.88]
Garza 2024	43	306	12	306	13.1%	4.01 [2.07, 7.76]
Gu 2024	19	152	2	152	6.9%	10.71 [2.45, 46.86]
Karlson 2024	57	579	16	281	13.9%	1.81 [1.02, 3.21]
Kobori 2023	11	205	1	205	4.5%	11.57 [1.48, 90.44]
Meluban 2024	11	65	19	2045	12.0%	21.72 [9.86, 47.87]
Nadeem 2024	125	922	788	34261	16.5%	6.66 [5.45, 8.15]
Peng 2024	8	104	1	49	4.3%	4.00 [0.49, 32.91]
Silveira 2023	11	205	1	205	4.5%	11.57 [1.48, 90.44]
Stark 2022	4	59	2	118	5.7%	4.22 [0.75, 23.73]
Wu 2024	17	90	5	102	9.9%	4.52 [1.59, 12.81]
Total (95% CI)		**2771**		**37808**	**100.0%**	**5.56 [3.35, 9.23]**
Total events	317		851			

Heterogeneity: Tau² = 0.39; Chi² = 35.18, df = 10 (P = 0.0001); I² = 72%
Test for overall effect: Z = 6.65 (P < 0.00001)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours Users Favours Non-users

Aborted procedures 1% in GLP-1RA users versus 0.3% in non-users (OR 5.13)

Adverse events higher in users (0.3%) compared to non-users (0.1%) (OR 4.04)

Pooled rates of bronchial aspiration similar (0.3% vs 0.25%; OR 1.75)

Conclusion: Use of GLP-1RAs is associated with increased retention of gastric contents and more frequent aborted procedures during upper endoscopy with comparable safety profile

Clinical Gastroenterology and Hepatology

Effects of Glucagon-Like Peptide-1 Receptor Agonists on Upper Gastrointestinal Endoscopy: A Meta-Analysis

Short Title: GLP-1 RA and Endoscopy

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ABSTRACT

Background and aims: Limited evidence exists regarding the impact of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on upper endoscopy. Therefore, a meta-analysis was conducted to comprehensively review the available evidence on this subject.

Methods: A systematic bibliographic search was carried out until May 2024. Pooled estimates were analyzed using a random-effects model, with results presented as odds ratios (OR) and 95% confidence intervals (CI). The primary outcome assessed was the rate of retained gastric content (RGC), while secondary outcomes included rates of aborted and repeated procedures, adverse event (AE) rate, and rates of aspiration.

Results: This analysis included 13 studies involving a total of 84,065 patients. Patients receiving GLP-1RA therapy exhibited significantly higher rates of RGC (OR 5.56, 3.35-9.23), a trend that was consistent among patients with diabetes (OR 2.60, 2.23-3.02). Adjusted analysis, accounting for variables such as sex, age, body mass index (BMI), diabetes, and other therapies, confirmed the elevated rates of RGC in the GLP-1RA user group (aOR 4.20, 3.42-5.15). Furthermore, rates of aborted and repeated procedures were higher in the GLP-1RA user group (OR 5.13, 3.01-8.75, and OR 2.19, 1.43-3.35; respectively). However, no significant differences were found in AE and aspiration rates between the two groups (OR 4.04, 0.63-26.03, and OR 1.75, 0.64-4.77; respectively).

Conclusion: Use of GLP-1RAs is associated with increased retention of gastric contents and more frequent aborted procedures during upper endoscopy. However, the AEs and aspiration rates do not seem different, therefore adjusting fasting time instead of routinely withholding GLP-1RAs could be reasonable in these patients.

Key words: Diabetes; Gastroscopy; Aspiration; Complication; Adverse event.

WHAT YOU NEED TO KNOW:

BACKGROUND: Limited evidence exists regarding the impact of GLP-1RAs on upper endoscopy

FINDINGS: Patients receiving GLP-1RAs exhibited significantly higher rates of RGC and of aborted and repeated procedures; however, no significant differences were found in AEs and aspiration rates

IMPLICATIONS FOR PATIENT CARE: The actual clinical impact of GLP-1RAs on upper endoscopy seems limited. Prolonging the duration of fasting for solids instead of routinely suspending GLP-1RAs could represent the optimal approach in these patients.

INTRODUCTION

The class of drugs known as glucagon-like peptide-1 receptor agonists (GLP-1RAs) was originally developed for the management of type 2 diabetes mellitus (T2DM). However, in recent years, the use of GLP-1RAs has expanded to include the promotion of weight loss[1]. GLP-1RAs mimic incretins, stimulate insulin secretion after a glucose load, and induce early satiety through delayed gastric emptying[2].

The impact of GLP-1RAs on slowing gastric motility has raised concerns in patients undergoing endoscopic procedures, particularly upper endoscopies. This is due to the perceived risk of aspiration of retained gastric contents in sedated patients and the decreased visibility of the gastric mucosa, which can reduce the diagnostic yield of the examination.

Despite limited available data, the American Society of Anesthesiologists (ASA) has recently issued consensus-based perioperative guidance suggesting that GLP-1RAs should be withheld prior to the procedure or surgery, regardless of the indication (T2DM or weight loss), dose, or the type of procedure/surgery[3].

The American Gastroenterology Association (AGA) has recommended an individualized approach to managing patients on GLP-1 RAs in the pre-endoscopic setting, citing the scarce data supporting this policy. The AGA emphasized the importance of not withholding the therapy in patients who do not exhibit symptoms suggesting retained gastric contents, such as nausea, vomiting, dyspepsia, or abdominal distention.

Both society documents underscored the urgent need for clinical data to inform clinical practice on this crucial topic. A recent meta-analysis showed a mild gastric emptying delay (~36 minutes per $T_{1/2}$) on solid phase scintigraphy and no significant differences on modalities reflective of liquid emptying with GLP-1 RA use[5]. However, this meta-analysis could not draw definitive conclusions due to limited clinical studies assessing retained gastric content and the risk of aspiration.

The aim of our meta-analysis was to determine the clinical impact of GLP-1 RAs on patients undergoing upper endoscopy procedures based on clinical outcomes such as rates of retained gastric contents (RGC), incidence of aborted procedures with consequent need for repeat endoscopy, and adverse events including the risk of bronchial aspiration.

MATERIALS AND METHODS

Selection criteria

Articles included in this meta-analysis were comparative studies fulfilling the following inclusion criteria and PICO format: (P) patients undergoing upper gastrointestinal endoscopy; (I) intervention, patients in GLP-1RA therapy; (C) comparator, patients non in GLP-1RA therapy; (O) outcomes, main outcomes were RGC and aspiration rate. Case reports, non-endoscopic studies, review articles, and non-comparative studies were excluded.

Search strategy

Figure 1 reports the search strategy followed in the meta-analysis. A systematic bibliographic search was conducted using major databases including PubMed, EMBASE, Cochrane Library and Google Scholar for studies fulfilling the inclusion criteria and published until May 2024. The search string used in our meta-analysis was: (((glp-1) OR (semaglutide)) OR (dulaglutide)) OR (liraglutide)) AND (endoscopy).

Relevant reviews and meta-analyses in the field were examined for additional eligible studies. Corresponding authors of included studies were contacted to obtain full text or further information when needed. Data extraction was conducted by two reviewers (AF and DR) and the quality of included studies was assessed by two authors independently (AF, DR) according to the Newcastle-Ottawa scale for non-randomized studies[6]. Disagreements were solved by discussion and following a third opinion (LF).

Outcomes

The primary outcome was the rate of RGC, defined mainly as food/solid contents retained in the stomach as assessed during gastroscopy. Secondary outcomes were the rate of aborted procedures (defined as procedures interrupted due to retained gastric content/risk of aspiration), rate of repeated endoscopy, and rates of adverse events, specifically rates of bronchopulmonary aspiration following endoscopy.

Statistical analysis

Diagnostic outcomes were pooled and compared between the two groups through a random-effects model based on Der Simonian and Laird test. Results were expressed in terms of odds ratio (OR) and 95% confidence intervals (CIs)[7].

We also performed a sensitivity analysis for the primary outcome based on type of study (whether full texts vs conference abstracts), duration of fasting before endoscopy (< 12 hours vs >12 hours), and restricted to studies conducted with propensity score matching and restricted to patients with diabetes. Moreover, to account for possible confounders, adjusted ORs (mainly based on clinical features including age, sex, body mass index [BMI], diabetes, and other therapies) were pooled and analyzed.

Chi-square and I^2 tests were used to compare the percentage of variability attributable to heterogeneity beyond chance across studies. $P<0.05$ for chi-square test and $I^2<20\%$ were interpreted as low-level heterogeneity. The probability of publication bias was assessed through visual inspection of funnel plots for the primary outcome, whereas it could not be assessed for the secondary outcomes due to the limited number of studies.
Number needed to scope was calculate to assess the number of procedures needed to observe 1 case of aborted and repeated procedures and 1 case of aspiration.

The quality of evidence was based upon GRADE criteria. Briefly, evidence from observational studies started at low quality, and was further rated down for the presence of any of the following factors – risk of bias in the literature, inconsistency (high heterogeneity in the estimates), indirectness, imprecision (wide 95% CIs crossing the unity or failure to reach the optimal information size), and publication bias[8].

All statistical analyses were conducted using RevMan version 5 from the Cochrane collaboration group. For all calculations a two-tailed p value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of included studies

Out of 177 studies initially identified, following preliminary exclusion of manuscripts not fulfilling inclusion criteria, 26 potentially relevant articles were examined [**Figure 1**]. After further screening and removing non-comparative studies or series not reporting outcomes of interest, 13 studies with 84,065 patients were included for meta-analysis[9-21].

The main characteristics of the included studies were reported in **Table 1**. The recruitment period ranged from 2015 to 2023. All included studies were retrospective comparative series, mainly conducted in the USA. Four studies were published as conference abstracts[15-18]. The two treatment arms were well balanced in terms of baseline factors such as age and sex. Adjustment for potential confounders including age, sex, BMI, diabetes, and other treatments was conducted in all studies except two series[15,18]. Propensity score matching based on the aforementioned variables was performed in 5 studies[11,13,17,19,20]. The definition of RGC varied slightly across included studies, however it was considered consistent as it was mainly based on visual inspection of food/solid contents retained in the stomach during gastroscopy. Duration of fasting before endoscopy was ≥12 hours in 2 studies[11,14], between 6 and 10 hours in 3 studies[10,13,19], while it was not reported in the other series.

Different GLP-1RA drugs were used in the included studies where semaglutide was used in two studies[10,17].
Quality was deemed mainly high with only 2 retrospective studies determined to be of low-quality[15,18].

Details on methodological characteristics and quality of included articles are shown in **Supplementary Table 1**.

Retained gastric contents

Based on 11 studies (2,771 GLP-1RA users and 37,808 non-users)[9-19], rates of RGC were significantly higher in patients on GLP-1RA therapy (OR 5.56, 3.35-9.23), with high heterogeneity (I^2=72%) (**Figure 2** and **Table 2).**

Subgroup analysis based on the type of publication and restricted to studies with propensity score matching confirmed the results of the main analysis but with considerably lower heterogeneity. As reported in **Table 2**, meta-analysis of full text papers reported an OR of 6.23 (5.18-7.49), with no heterogeneity (I^2=0%).

Sensitivity analysis of 4 studies conducted with propensity score matching (747 patients in each group)[11,13,17,19] confirmed clinically significant rates of RGC in GLP-1RAs users (OR 4.59, 2.73-7.72), with no heterogeneity (I^2=0%). Further sensitivity analysis restricted to only patients with diabetes (4 studies with 7,287 patients) also confirmed the primary findings (OR 2.60, 2.23-3.02) with non-significant heterogeneity (I^2=24%). Similar results were observed also in sensitivity analysis based on duration of fasting before endoscopy (OR 5.47, 2.16-13.87 with at least 12 hours vs OR 4.07, 2.33-7.09 with less than 12 hours of fasting). Again, no heterogeneity was observed in sensitivity analysis based on duration of fasting (I^2=0%).

As reported in **Table 2** and **Figure 3**, pooled analysis of adjusted ORs based on 6 studies with 36,736 patients[9,10,12-14,19] and accounting for several variables including sex, age, BMI, diabetes and other therapies, confirmed the higher rate of RGC in the group of GLP-1RAs users (aOR 4.20, 3.42-5.15) with no evidence of heterogeneity (I^2=0%). No evidence of publication bias was observed as depicted in the funnel plots, see **Supplementary Figures 1a** and **1b**.

Secondary outcomes and quality of evidence

Five studies[9,12,16,18,19] with 1,748 patients in the GLP-1RAs group and 34,793 patients in the control group reported rates of aborted procedures. The pooled rate of aborted procedures was 1% (0.6%-2%) in GLP-1RA users and 0.3% (0.2%-0.4%) in non-users. The meta-analysis showed this rate was significantly higher in the GLP-1RA group (OR 5.13, 3.01-8.75), with no evidence of heterogeneity (I^2=0%) (**Supplementary Figure 2**). Number needed to scope to observe one case of aborted procedure was 110 (95% CI: 50-400).

Three studies[9,12,18] with 1,085 patients in the GLP-1RA group and 34,428 patients in the control group reported the rates of repeated procedures. The pooled rates of repeated procedures were 2% (1.5%-3%) and 1% (0.8%-1.3%) in the two groups, respectively. As shown in the **Supplementary Figure 3**, GLP-1RAs users had a significantly higher need for repeated procedures (OR 2.19, 1.43-3.35), with no heterogeneity (I^2=0%). Number needed to scope for repeated procedures was 120 (95% CI: 50-600).

AEs were reported in 4 studies[9,10,13,14] with 1,351 and 35,040 patients in the two groups, respectively. The pooled rate of AEs was 0.3% (0.001%-0.7%) in GLP-1RA users and 0.1% (0.18%-0.25%) in non-users. As depicted in **Supplementary Figure 4**, there was no significant difference in terms of AE rate between the two groups (OR 4.04, 0.63-26.03), with non-significant moderate heterogeneity (I^2=55%).

Six studies[9,10,13,14,20,21] with 19,842 GLP-1RAs users and 60,035 non-users reported rates of bronchial aspiration. Pooled rates of bronchial aspiration were 0.3% (0.001%-0.1%) and 0.2% (0.001%-1%), respectively. As shown in **Figure 4**, there was no significant difference between the two groups (OR 1.75, 0.64-4.77) with evidence of heterogeneity (I^2=61%). Number needed to scope to observe one event of aspiration was 794 (95% CI: -500 to 950).

As reported in supplementary Table 2, the quality of evidence concerning all outcomes was rated as very low because the meta-analysis was based on non-randomized retrospective studies as well as the risk of bias in the literature, indirectness (different study design or protocols for fasting before endoscopy) and imprecision (wide 95% intervals crossing the unity or failure to reach the optimal information size).

DISCUSSION

GLP-1RAs are increasingly being used to treat T2DM and, more recently, for managing obesity. These agents work through various mechanisms, including regulating insulin production by pancreatic cell islets, controlling appetite and satiety, and affecting the gastrointestinal tract's motility and accommodation[22]. Their well-known effect on delaying gastric emptying and motility has raised concerns in patients undergoing upper and lower endoscopy, particularly in deep sedation, due to the risk of bronchopulmonary aspiration and reduced diagnostic yield because of retention of gastric content[3].

A recent meta-analysis highlighted the delayed gastric kinetics caused by the use of GLP-1RAs but could not definitively conclude on the clinical effects of delayed gastric emptying due to the lack of data[5]. Similarly, both the ASA and AGA documents emphasized the need for data to inform clinical practice in this field, basing their conclusions solely on expert consensus[3,4].

Through a meta-analysis of 13 studies, we made several key observations. First, rates of RGC were significantly higher in patients under GLP-1RA therapy (OR 5.56, 3.35-9.23). This finding is a direct consequence of the delayed gastric emptying and kinetics demonstrated in several studies conducted using scintigraphy and gastric ultrasound[5]. RGC can significantly affect the quality of the procedure. However, it is important to understand that the clinical impact of solid and liquid gastric emptying is different. The normal stomach secretes up to 2–3 L of fluid/day but this is less of an issue as liquid can easily be removed during an esophagogastroduodenoscopy. In

fact, previous studies found RGC might not represent an issue in patients undergoing combined esophagogastroduodenoscopy and colonoscopy, unlike esophagogastroduodenoscopy alone, presumably because of fasting and consumption of only a liquid diet the day before the procedures[10,20].

The definition of RGC, although slightly different across the included studies, relied on solid content in the stomach as this could impair the quality of the procedure and increase the risk of aspiration. However, the amount of these contents and their clinical impact may be variable. Therefore, an individualized approach based on the indication of GLP-1RAs use (withholding the drug in patients with diabetes could lead to more harm than benefits, whereas non-diabetic patients with obesity could safely interrupt the drug before the procedure) and the presence of symptoms related to RGC could represent the best choice in this setting, as suggested by the AGA document[4]. It should be noted that including standard interruption of GLP-1RAs therapy in all patients undergoing endoscopic procedures would add more complexity to periprocedural management and exacerbate barriers while delaying care for patients requiring endoscopic procedures. Hence, this approach may not be effective in our daily clinical practice. Instead of stopping GLP-1RAs, a potential strategy could be to place patients on a liquid diet the day before endoscopy thus prolonging the duration of fasting for solid for at least 12 hours, particularly in the case of longer and more complex procedures that would require deep sedation such as endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound (EUS) where the risk of aspiration could be higher. Of note, sensitivity analysis based on duration of fasting before endoscopy did not find a decreased rate of RGC in GLP-1RA users when fasting was at least 12 hours; however, this finding should be interpreted with caution due to the very limited number of studies in this subgroup and the wide 95% CIs that make the results imprecise; therefore, further large series are needed to assess this important clinical issue.

Secondly, in our meta-analysis, higher rates of RGC were independent of other potential confounders, such as diabetes or the use of other drugs that could delay gastric emptying. In fact, multiple sensitivity analyses and the adjusted OR confirmed the findings of the primary analysis but with decreased heterogeneity. Evidently, the inclusion of different kinds of studies (both full text papers and conference abstracts) and with different methodology (propensity score matching vs other forms of adjustments vs unadjusted analysis) represented main sources of the high heterogeneity observed in the main analysis (I^2=72%) that in fact decreased when performing the sensitivity analysis based on these methodological parameters. Therefore, the effects on gastric kinetics and emptying are due to GLP-1RAs themselves regardless of the underlying indication for this therapy or concomitant drugs.

The third finding of our study was the increased rate of aborted and repeated procedures in the group of GLP-1RAs users. GLP-1RAs led to a significantly increased rate of aborted endoscopies (OR 5.13, 3.01-8.75) and higher need for repeat procedures (OR 2.19, 1.43-3.35), although these results should be interpreted with caution as based on a limited number of studies. Moreover, a subgroup analysis restricted to patients with diabetes was not feasible for these secondary outcomes due to the low number of available studies. Of note, the rate of aborted and repeat

procedures in the included studies was low, with a reported rate of 1.5% and 2.4%, respectively, in the largest series[9]. This meant that only every 110 patients undergoing upper endoscopy while in GLP-1RA therapy we would observe an aborted procedure and only every 120 patients we would need to repeat the procedure. Therefore, as previously mentioned, an individualized approach suggested by the AGA task force[4] could represent the best compromise as the implications of the above findings do not seem to be very impactful in clinical practice.

Fourth, the rates of adverse events, especially aspiration, did not seem to show a statistically significant difference between the two groups but only a possible increase (OR 4.04, 0.63-26.03 and OR 1.75, 0.64-4.77; respectively). Of note, the high imprecision in these results based on wide 95% CIs was probably related to the limited number of studies and low incidence of these events, thus requiring larger series to confirm these findings. Moreover, the limited data on newer and more potent GLP-1RAs such as semaglutide or tirzepatide calls for a note of caution in this regard and prevents us from drawing a definitive conclusion on the safety of these class of drugs. The main reason behind the ASA's cautionary statement regarding the use of GLP-1RA was the purportedly elevated incidence of bronchial aspiration following upper endoscopy[3]. A large retrospective analysis using the TriNetX database showed significantly higher rates of aspiration pneumonia in GLP-1RAs users undergoing upper or combined upper-lower endoscopy while no difference was observed in patients undergoing lower endoscopy alone[20]. On the other hand, the analysis of the large MarketScan administrative claims databases[21] found that GLP1-RA use is not associated with increased risk of pulmonary complications after upper endoscopy compared to other hypoglycemic medications in patients with diabetes and a recent analysis of the Mayo Health System database found only 2 cases of pulmonary aspiration out of 4,134 upper endoscopic procedures conducted in GLP-1RAs users[23]. Likewise, another recent retrospective American series found only 2 cases of aspiration out of 1512 patients undergoing upper endoscopy[24]. Results of these large database studies should always be interpreted with caution due to the retrospective design and the lack of granularity. On the other hand, the relatively low rate of this dreadful event requires very large series to assess the real incidence and the potential impact of GLP-1RAs in this setting. In fact, number needed to scope to observe an event of bronchial aspiration was 794, with no difference between the two groups (95% CIs crossing 1). Based on our analysis, with the aforementioned caveats in the interpretation of our findings and pointing out the pressing need for large prospective studies, the strategy of routinely withholding GLP-1RAs in patients undergoing upper endoscopy is not justified as a higher risk of pulmonary aspiration was not observed. Unfortunately, a subgroup analysis based on duration of fasting was not feasible due to the lack of data; however, it seems reasonable that the aforementioned approach to prolong fasting for solids for at least 12 hours before endoscopy could represent a reasonable approach. The quality of evidence was rated as very low and further studies, preferably RCTs, are needed to draw definitive conclusions on this topic.

Our study has limitations. Firstly, the inclusion of a limited number of studies and the use of heterogeneous sample sizes and methodologies require caution in interpreting our findings. Particularly, all the included studies were retrospective and some of them were published only as conference abstracts. However, we performed several sensitivity analyses and a specific meta-analysis of adjusted results, which confirmed the main findings and

thoroughly explored the sources of observed heterogeneity. Of note, prospective studies are difficult to conduct as they would require a large series of patients to capture the real incidence of uncommon outcomes such as aspiration or aborted procedures. Secondly, some important clinical outcomes, such as aspiration or the rate of aborted procedures, were reported only in a subgroup of studies and with a limited incidence. Thus, further evidence is warranted to strengthen our results that currently appear imprecise for drawing definitive conclusions. Thirdly, a subgroup analysis based on the type, dosage, and duration of GLP-1RA usage was not feasible due to the lack of data, so our results should be considered applicable to the entire class of drugs, while specific indications tailored to individual patients, for example to patients with diabetes, cannot be made based on the current evidence. Specifically, only few studies examined the effects of newer more potent agents such as semaglutide or tirzepatide and our meta-analysis was not powered for these analyses. Moreover, the included studies did not compare or examine protocol changes to GLP-1RA use before upper GI endoscopy. Further large series are needed to address these points. Fourth, most of the included studies were conducted in the USA where there is a different setting for example concerning the use of deep sedation or the availability of the anesthesiologists in the endoscopy facilities. The included studies did not specify which kind of sedation was used; however, only a very limited proportion of patients underwent endoscopy intubated or in general anesthesia. Fifth, the definition of RGC, although mainly based on retention of solid content, was not standardized nor based on quantitative measures, thus limiting the clinical implications of our findings. Finally, the cost implications of the two proposed strategies, whether to routinely suspend GLP-1RAs or take a more individualized approach, were beyond the scope of our study and should be assessed through robust cost-effectiveness models.

Our comprehensive analysis indicates that while the use of GLP-1RA results in higher rates of RGC, the actual clinical impact appears to be limited. Therefore, there is no strong evidence to support the routine discontinuation of the drug before upper endoscopy procedures. Additionally, the incidence of adverse events, particularly aspiration, is low and not significantly different between the two groups. Hence, prolonging the duration of fasting for solids could represent the optimal approach in these patients although this strategy requires further evaluation.

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FIGURE LEGENDS

Figure 1. Flow chart of the included studies.

Figure 2. Forest plot comparing the rate of retained gastric content

The rate of retained gastric content was significantly higher in the group of patients using GLP-1 RA (OR 5.56, 3.35-9.23; $p<0.00001$), with high evidence of heterogeneity ($I^2=72\%$).

Figure 3. Forest plot pooling adjusted odds ratio for retained gastric content

Pooled adjusted odds ratio was 4.20 (3.42-5.15; p<0.00001) with no evidence of heterogeneity (I^2=0%). Adjustment was for several variables including sex, age, BMI, diabetes, other therapies.

Figure 4. Forest plot comparing the aspiration rate in the two study groups

The rate of aspiration was not significantly different between the two groups (OR 1.75, 0.64-4.77), with evidence of heterogeneity (I^2=61%).

Table 1. Characteristics of included studies

Study	Arms	Sample size	Study period/ Design	Country	Age	Sex male	Diabetes	Methodology	Definition of retained gastric content/ Duration of fasting before endoscopy/ Sedation	GLP-1 RA used/ Duration of use
Nadeem 2024[9]	GLP-1 RA users Non-users	922 34261	2019-2023/ Retrospective	USA	57.1±12.9 53.9±17.5	39% 41%	82% 16%	Adjustment for age, sex, race, diabetes, BMI	NR/ NR/ NR	NR/ NR
Silveira 2023[10]	GLP-1 RA users Non-users	33 371	2021-2022/ Retrospective	Brazil	NR	NR	NR	Inverse probability treatment weighting for several variables including age, sex, diabetes, BMI	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/ at least 8 h fasting for solids and fluids/ 97% deep sedation 3% general anesthetic	Semaglutide/ NR
Kobori 2023[11]	GLP-1 RA users Non-users	205 205	2020-2022/ Retrospective	Japan	70 (62-76) 72 (63-77)	79.5% 78.9%	100% 100%	Propensity score matching for HbA1c, age, sex and insulin treatment	Any solid content in the stomach/ At least 12 hours/ NR	NR/ NR
Stark 2022[12]	GLP-1 RA users Non-users	59 118	2015-2020/ Retrospective	USA	64±10 66±10.2	83% 94%	97% 98%	Matching for diabetes and cirrhosis	Documented food retention/ NR/ NR	Dulaglutide 56% Liraglutide 37%/ NR

Garza 2024[13]	GLP-1 RA users Non-users	306 306	2018-2023/ Retrospective	USA	61 (52-68) 62 (51-70)	51% 50%	88% 88%	Propensity score matching for age, sex, BMI, diabetes, complications of diabetes, insulin use	Any solid content in the stomach/ At least 7 hours/ Sedation	Dulaglutide 35% Semaglutide 36% Liraglutide 19% Other 14%/ NR
Wu 2024[14]	GLP-1 RA users Non-users	90 102	2019-2023 Retrospective	USA	64.1 (56.6-68.9) 58.5 (45.7-67.6)	38% 47%	69% 25%	Adjustment for several variables including age, sex, BMI, diabetes, antidiabetic therapy	NR/ At least 12 hours/ Sedation 87% General anesthesia 13%	NR/ 329 (182-646) days
Meluban 2024[15a]	GLP-1 RA users Non-users	65 2045	2022-2023 Retrospective	USA	NR	NR	NR	Unadjusted analysis	Any solid content/ NR/ NR	Semaglutide 60% Dulaglutide 26.1% Tirzepatide 4.6% Liraglutide 9.2%/ NR
Karlson 2024[16a]	GLP-1 RA users Non-users	579 281	2015-2023 Retrospective	USA	NR	NR	NR	Matching by age, diabetes, BMI, therapy	NR/ NR/ Sedation	NR/ NR
Gu 2024[17a]	GLP-1 RA users Non-users	152 152	2022-2023 Retrospective	USA	57.8±11.8 57.2±12.8	NR	NR	Propensity score matching	NR/ NR/ NR	Semaglutide 100%/ 4.7±4 months
Peng 2024[18a]	GLP-1 RA users Non-users	104 49	2023 Retrospective	USA	55±8 60±10	26% 29%	89% 80%	Unadjusted analysis	NR/ NR/ NR	Liraglutide 87% Semaglutide 13%/ NR
Chapman 2024[19]	GLP-1 RA users Non-users	84 84	2017-2023 Retrospective	USA	53.9±12.3 54±11.8	71.4% 69%	86.9% 84.5%	Propensity score matching for confounders	POLPREP score/ Median 10 hours/ Sedation 93.5%	Dulaglutide 49% Semaglutide 24% Liraglutide 17% Others 10%/

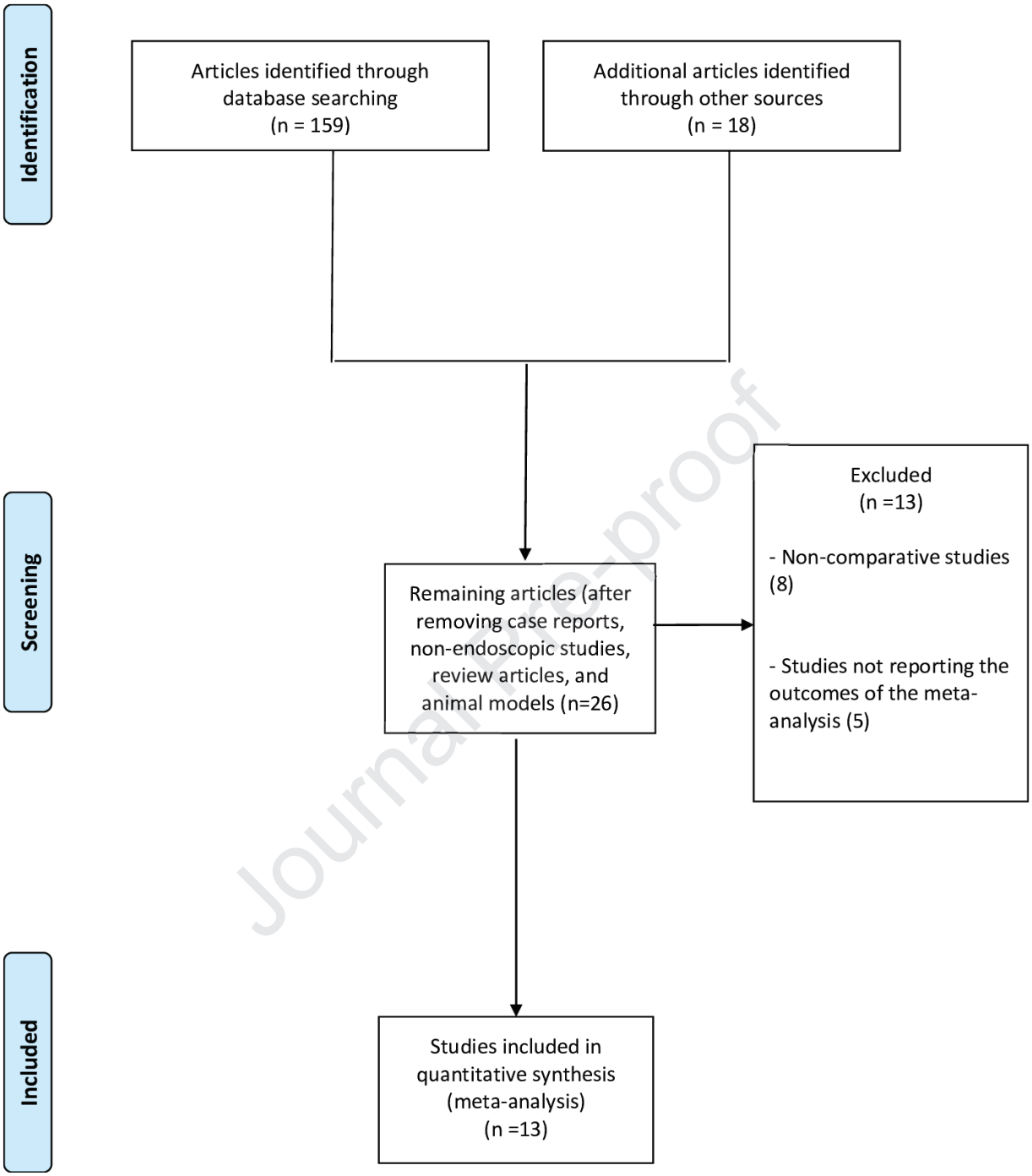
									General Anesthesia 6.5%	331 (132-535) days
Yeo 2024[20b]	GLP-1 RA users Non-users	3372 3331	2018-2020 Retrospective	USA	55.4±8.38 55.6±8.82	44.2% 44.2%	89.2% 91.9%	Propensity score matching for several variables including age, sex, BMI, diabetes, antidiabetic therapy	NR* NR NR	NR/ >6 months
Barlowe 2024[21b]	GLP-1 RA users Non-users	15119 21664	2005-2021 Retrospective	USA	55 (49-60) 57 (52-61)	40% 48%	100% 100%	Propensity score weighting for age, sex, other comorbidities	NR* NR NR	NR/ NR

Data are reported as absolute numbers (percentages) or mean (± standard deviation or with interquartile range)
[a]Study published only as a conference abstract
[b]Only patients undergoing upper endoscopy were included in the analysis
* Not assessed as an outcome of this study
Abbreviations: BMI, Body Mass Index; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; NR, Not Reported

Table 2. Overall and sensitivity analysis of the retained gastric content rate. Sensitivity analysis was performed based on the study design (propensity score matching), the type of publication (full text vs conference abstract), diabetes, duration of fasting before endoscopy (less than 12 hours vs at least 12 hours), and pooling the adjusted odds ratio

Subgroup	No. of Cohorts	No. of patients	Odds ratio (95% CI)	Within-group heterogeneity (I^2)
Retained gastric content rate				
Overall	11	40579	5.56 (3.35-9.23)	72%
Full text papers	7	37152	6.23 (5.18-7.49)	0%
Conference abstracts	4	3427	6.44 (1.34-30.95)	89%
Propensity score matching	4	1494	4.59 (2.73-7.72)	0%
Diabetes	4	7287	2.60 (2.23-3.02)	24%
Fasting at least 12 hours	2	602	5.47 (2.16-13.87)	0%
Fasting less than 12 hours	3	1190	4.07 (2.33-7.09)	0%
Adjusted odds ratio	6	36736	4.20 (3.42-5.15)	0%

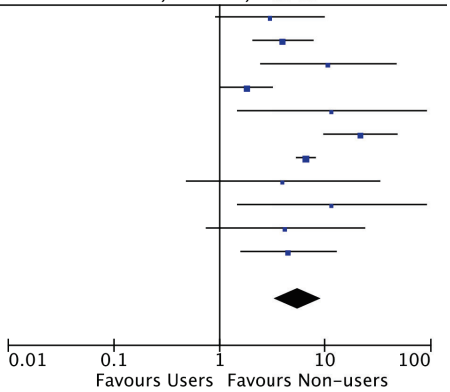
Abbreviation: CI, Confidence Interval



Study or Subgroup	Users Events	Users Total	Non-users Events	Non-users Total	Weight	Odds Ratio M-H, Random, 95% CI
Chapman 2024	11	84	4	84	8.8%	3.01 [0.92, 9.88]
Garza 2024	43	306	12	306	13.1%	4.01 [2.07, 7.76]
Gu 2024	19	152	2	152	6.9%	10.71 [2.45, 46.86]
Karlson 2024	57	579	16	281	13.9%	1.81 [1.02, 3.21]
Kobori 2023	11	205	1	205	4.5%	11.57 [1.48, 90.44]
Meluban 2024	11	65	19	2045	12.0%	21.72 [9.86, 47.87]
Nadeem 2024	125	922	788	34261	16.5%	6.66 [5.45, 8.15]
Peng 2024	8	104	1	49	4.3%	4.00 [0.49, 32.91]
Silveira 2023	11	205	1	205	4.5%	11.57 [1.48, 90.44]
Stark 2022	4	59	2	118	5.7%	4.22 [0.75, 23.73]
Wu 2024	17	90	5	102	9.9%	4.52 [1.59, 12.81]
Total (95% CI)		**2771**		**37808**	**100.0%**	**5.56 [3.35, 9.23]**
Total events	317		851			

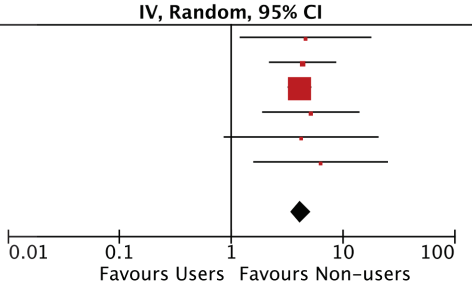
Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 35.18$, df = 10 (***P*** = .0001); $I^2 = 72\%$

Test for overall effect: Z = 6.65 (***P*** < .00001)



Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Chapman 2024	1.5304	0.6836	2.3%	4.62 [1.21, 17.64]
Garza 2024	1.4702	0.3455	9.1%	4.35 [2.21, 8.56]
Nadeem 2024	1.4061	0.116	80.5%	4.08 [3.25, 5.12]
Silveira 2023	1.639	0.5034	4.3%	5.15 [1.92, 13.81]
Stark 2022	1.4398	0.8057	1.7%	4.22 [0.87, 20.47]
Wu 2024	1.8405	0.6993	2.2%	6.30 [1.60, 24.81]
Total (95% CI)			**100.0%**	**4.20 [3.42, 5.15]**

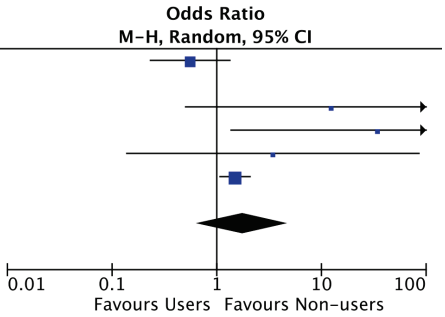
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.59$, df = 5 (*P*=.99); $I^2 = 0\%$
Test for overall effect: Z = 13.79 (*P*<.00001)



Study or Subgroup	Users Events	Users Total	Non-users Events	Non-users Total	Weight	Odds Ratio M-H, Random, 95% CI
Barlowe 2024	7	15119	18	21664	33.4%	0.56 [0.23, 1.33]
Garza 2024	0	306	0	306		Not estimable
Nadeem 2024	0	922	1	34261	8.1%	12.38 [0.50, 304.09]
Silveira 2023	1	33	0	371	8.0%	34.29 [1.37, 858.81]
Wu 2024	1	90	0	102	8.0%	3.44 [0.14, 85.40]
Yeo 2024	90	3372	60	3331	42.6%	1.49 [1.07, 2.08]
Total (95% CI)		**19842**		**60035**	**100.0%**	**1.75 [0.64, 4.77]**
Total events	99		79			

Heterogeneity: $Tau^2 = 0.59$; $Chi^2 = 10.32$, df = 4 (***P***= .04); $I^2 = 61\%$

Test for overall effect: Z = 1.09 (***P***= .27)



ONLINE SUPPLEMENT

Supplementary Table 1. Risk of bias assessment and quality of included studies.

	Observational studies[a]			
	Selection	**Comparability**	**Outcome**	**Overall quality**
Nadeem 2024	***	**	**	H
Silveira 2023	**	**	*	H
Kobori 2023	**	**	*	H
Stark 2022	**	**	*	H
Garza 2024	***	**	*	H
Wu 2024	**	**	*	H
Meluban 2024	*	*	*	L
Karlson 2024	**	**	*	H
Gu 2024	**	**	*	H
Peng 2024	*	*	*	L
Chapman 2024	**	**	*	H
Yeo 2024	**	**	*	H
Barlowe 2024	**	**	*	H

L, low; H, high; U, unclear; M, moderate.
[a] Study quality assessment performed by means of Newcastle/Ottawa scale (each asterisk represents if the respective criterion within the subsection was satisfied)

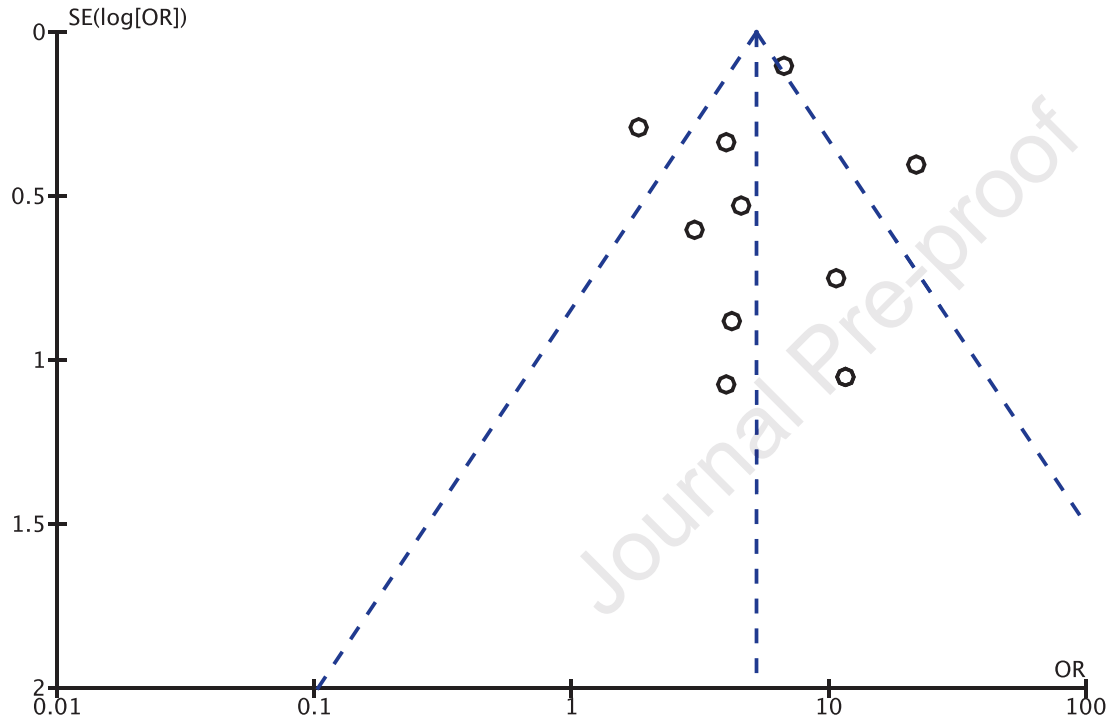
Supplementary Table 2. Table of evidence

Certainty assessment								Effect estimate	Certainty	Comments
Outcome	**No. of studies**	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**			
Retained gastric content	11	Observational	High	High	High	Low	Low	OR 5.56 (3.35-9.23)	◯◯◯◯◯ Very Low	High indirectness due to different regimens of fasting before endoscopy and different study design
Adjusted analysis for retained gastric content	6	Observational	Low	Low	High	Low	Low	aOR 4.20 (3.42-5.15)	◯◯◯◯◯ Very Low	Based on non-randomized studies, high indirectness due to different regimens of fasting before endoscopy
Aborted procedures	5	Observational Studies	High	Low	High	High	Low	OR 5.13 (3.01-8.75)	◯◯◯◯◯ Very Low	Based on non-randomized studies, high imprecision due to failure to reach the

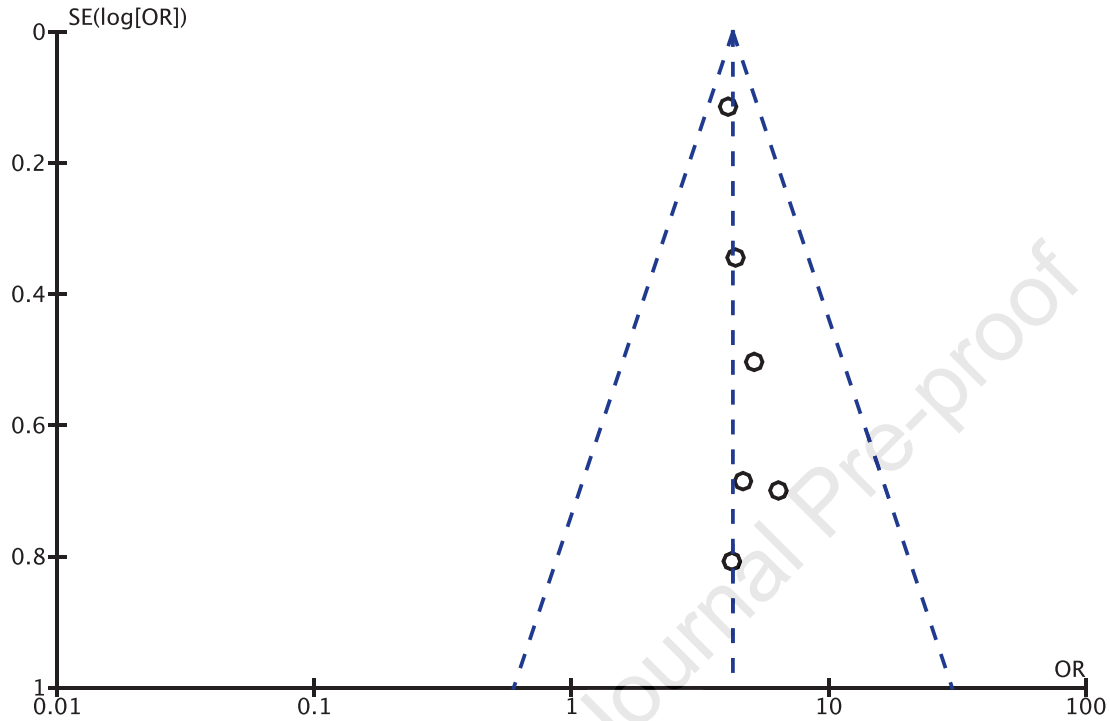
										optimal information size
Repeated procedures	3	Observational studies	High	Low	High	High	Low	OR 2.19 (1.43-3.35)	◯◯◯◯◯ Very Low	Based on non-randomized studies, high imprecision due to failure to reach the optimal information size
Adverse events	4	Observational studies	High	High	High	High	Low	OR 4.04 (0.63-26.03)	◯◯◯◯◯ Very Low	Based on non-randomized studies, high imprecision due to wide confidence intervals, high heterogeneity
Aspiration	6	Observational studies	High	High	High	High	Low	OR 1.75 (0.64-4.77)	◯◯◯◯◯ Very Low	Based on non-randomized studies, high imprecision due to wide confidence intervals, high heterogeneity

Supplementary Figure 1. Funnel plot for (a) retained gastric content rate and (b) adjusted odds ratio

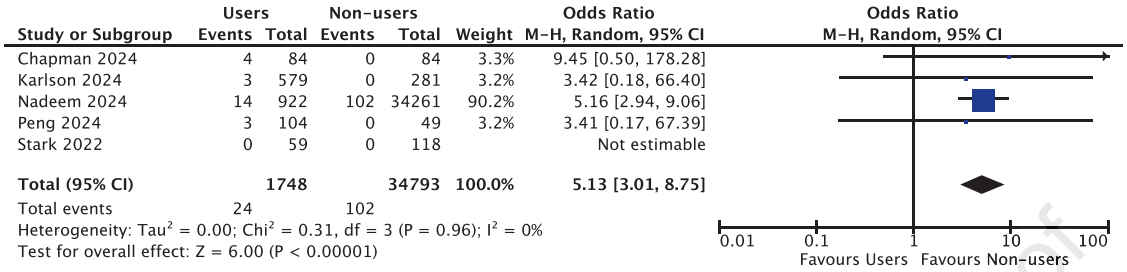
a)



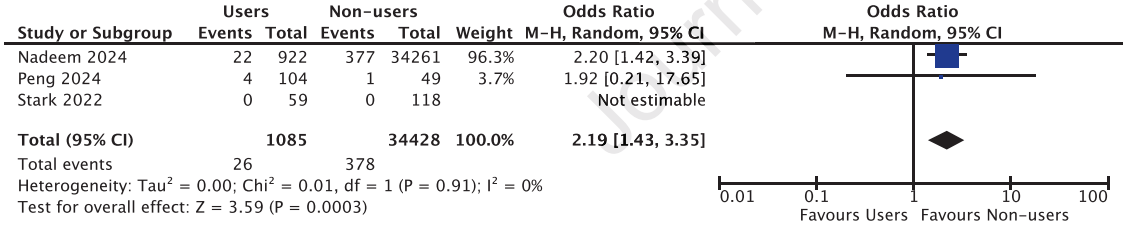
b)



Supplementary Figure 2. Forest plot for rate of aborted procedures



Supplementary Figure 3. Forest plot for rate of repeated procedures

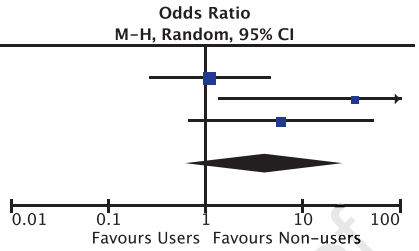


Supplementary Figure 4. Forest plot for adverse event rate

Study or Subgroup	Users Events	Total	Non-users Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Garza 2024	0	306	0	306		Not estimable
Nadeem 2024	2	922	68	34261	45.1%	1.09 [0.27, 4.47]
Silveira 2023	1	33	0	371	21.6%	34.29 [1.37, 858.81]
Wu 2024	5	90	1	102	33.3%	5.94 [0.68, 51.84]
Total (95% CI)		**1351**		**35040**	**100.0%**	**4.04 [0.63, 26.03]**
Total events	8		69			

Heterogeneity: $Tau^2 = 1.49$; $Chi^2 = 4.48$, df = 2 (P = 0.11); $I^2 = 55\%$

Test for overall effect: Z = 1.47 (P = 0.14)



Effects of Glucagon-Like Peptide-1 Receptor Agonists on Upper Gastrointestinal Endoscopy: A Meta-Analysis

Short Title: GLP-1 RA and Endoscopy

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WHAT YOU NEED TO KNOW:

BACKGROUND: Limited evidence exists regarding the impact of GLP-1RAs on upper endoscopy

FINDINGS: Patients receiving GLP-1RAs exhibited significantly higher rates of RGC and of aborted and repeated procedures; however, no significant differences were found in AEs and aspiration rates

IMPLICATIONS FOR PATIENT CARE: The actual clinical impact of GLP-1RAs on upper endoscopy seems limited. Prolonging the duration of fasting for solids instead of routinely suspending GLP-1RAs could represent the optimal approach in these patients.