SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

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

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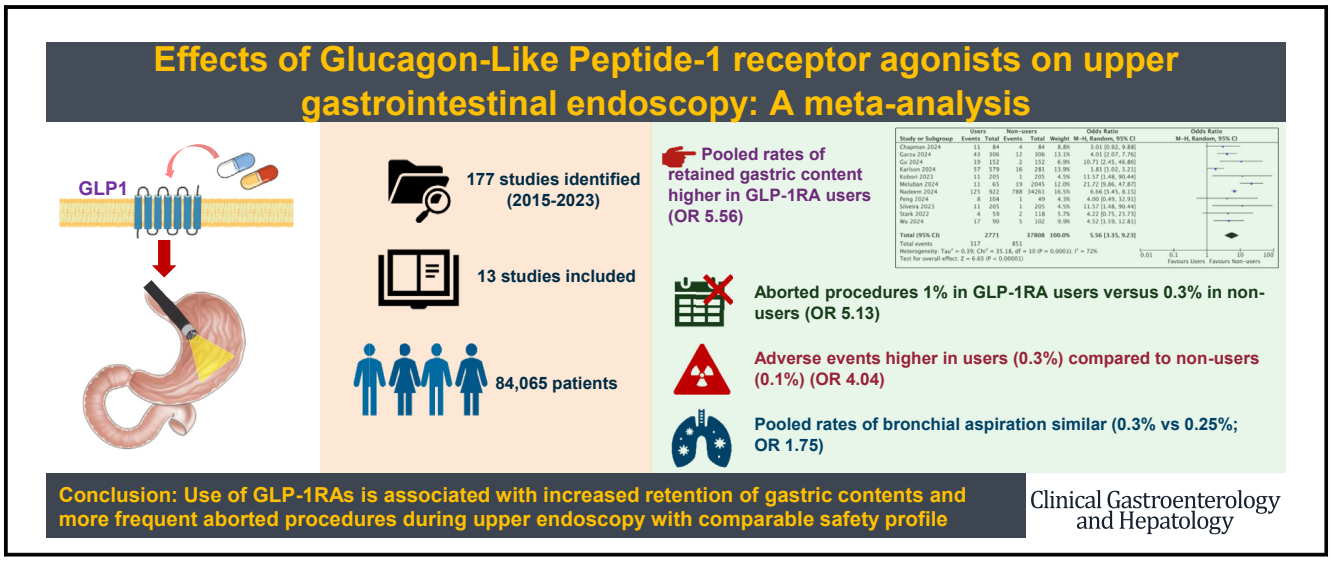

BACKGROUND AND AIMS: **Limited evidence exists regarding the impact of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on upper endoscopy. Therefore, a meta-analysis was conducted to comprehensively review the available evidence on this subject.**

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Abbreviations used in this paper: AE, adverse event; AGA, American Gastroenterological Association; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; OR, odds ratio; RGC, retained gastric content; T2DM, type 2 diabetes mellitus.

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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 ratio (OR) and 95% confidence interval (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 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; 95% CI, 3.35 to 9.23), a trend that was consistent among patients with diabetes (OR, 2.60; 95% CI, 2.23 to 3.02). Adjusted analysis, accounting for variables such as sex, age, body mass index, diabetes, and other therapies, confirmed the elevated rates of RGC in the GLP-1RA user group (adjusted OR, 4.20; 95% CI, 3.42 to 5.15). Furthermore, rates of aborted and repeated procedures were higher in the GLP-1RA user group (OR, 5.13; 95% CI, 3.01 to 8.75; and OR, 2.19; 95% CI, 1.43 to 3.35; respectively). However, no significant differences were found in AE and aspiration rates between the 2 groups (OR, 4.04; 95% CI, 0.63 to 26.03; and OR, 1.75; 95% CI, 0.64 to 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 adverse event and aspiration rates do not seem different; therefore, adjusting fasting time instead of routinely withholding GLP-1RAs could be reasonable in these patients.**

Keywords: Diabetes; Gastroscopy; Aspiration; Complication; Adverse Event.

See editorial on page 711.

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 content (RGC) 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 Gastroenterological 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 RGC, such as nausea, vomiting, dyspepsia, or abdominal distention.[4]

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 RGC 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 RGC, incidence of aborted procedures with consequent need for repeat endoscopy, and adverse events (AEs) 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 not in GLP-1RA therapy; (O) outcomes, main outcomes were RGC and aspiration rate. Case reports, nonendoscopic studies, review articles, and noncomparative 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 2 reviewers (A.F. and D.R.) and the quality of included studies was assessed by 2 authors independently (A.F., D.R.) according to the Newcastle–Ottawa scale for nonrandomized studies.[6] Disagreements were solved by discussion and following a third opinion (L.F.).

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 RGC/risk of aspiration), rate of

What You Need to Know

Background

Limited evidence exists regarding the impact of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on upper endoscopy.

Findings

Patients receiving GLP-1RAs exhibited significantly higher rates of retained gastric content and of aborted and repeated procedures; however, no significant differences were found in adverse event 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.

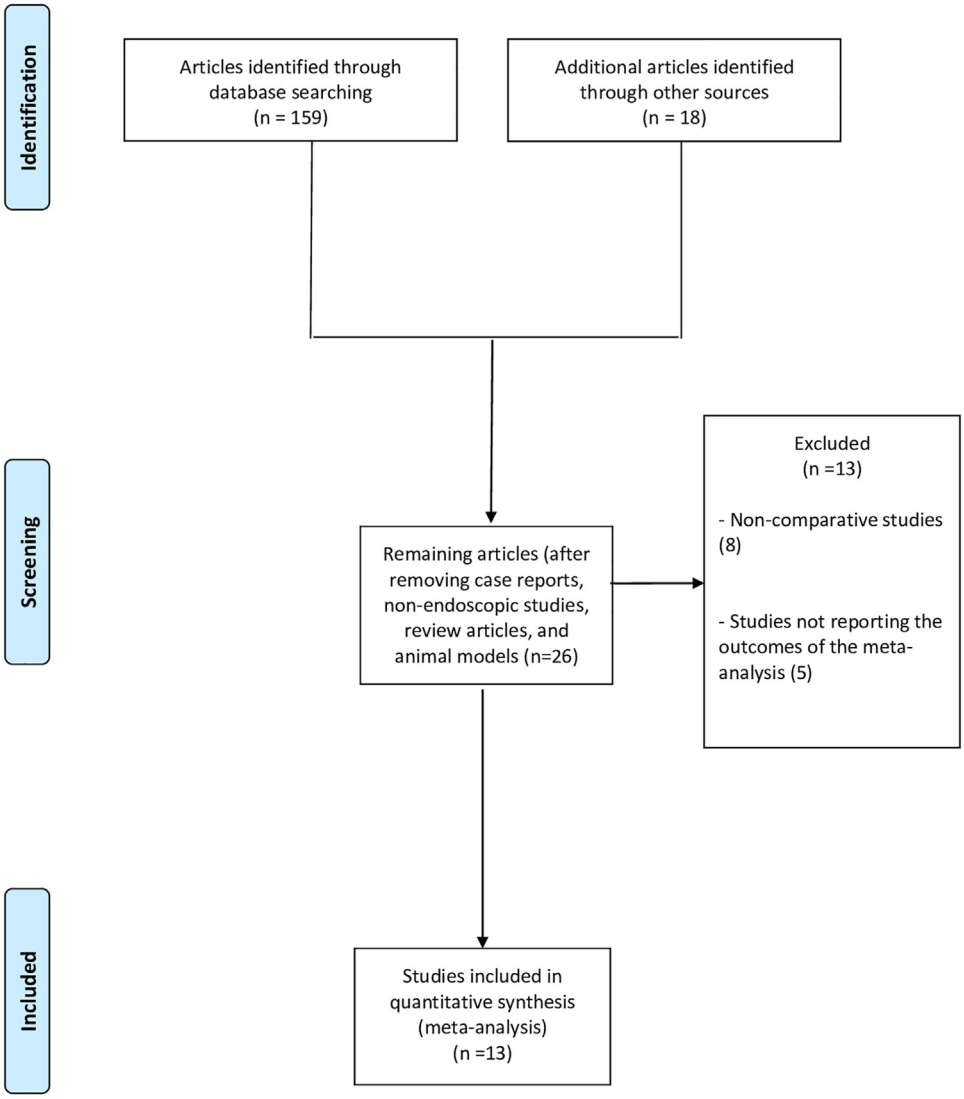

Figure 1. Flow chart of the included studies.

repeated endoscopy, and rates of RGC, specifically rates of bronchopulmonary aspiration following endoscopy.

Statistical Analysis

Diagnostic outcomes were pooled and compared between the 2 groups through a random-effects model based on the DerSimonian and Laird test. Results were expressed in terms of odds ratio (OR) and 95% confidence interval (CI).[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. $P < .05$ 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.

The 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 the 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 2-tailed P value of <.05 was considered statistically significant.

Results

Characteristics of Included Studies

Out of 177 studies initially identified, following preliminary exclusion of article 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 United States. Four studies were published as conference abstracts.[15–18] The 2 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 2 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] and not reported in the other series.

Different GLP-1RA drugs were used in the included studies in which semaglutide was used in 2 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 Content

Based on 11 studies (2771 GLP-1RA users and 37,808 nonusers),[9–19] rates of RGC were significantly higher in patients on GLP-1RA therapy (OR, 5.56; 95% CI, 3.35 to 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 articles reported an OR of 6.23 (95% CI, 5.18 to 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-1RA users (OR, 4.59; 95% CI, 2.73 to 7.72), with no heterogeneity ($I^2 = 0\%$). Further sensitivity analysis restricted to only patients with diabetes (4 studies with 7287 patients) also confirmed the primary findings (OR, 2.60; 95% CI, 2.23 to 3.02) with nonsignificant heterogeneity ($I^2 = 24\%$). Similar results were observed also in sensitivity analysis based on duration of fasting before endoscopy (ORs: with at least 12 hours of fasting 5.47 [95% CI, 2.16 to 13.87] vs with <12 hours of fasting 4.07 [95% CI, 2.33 to 7.09]). 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,

Table 1. Characteristics of Included Studies

Study	Arms	Sample Size	Study period/ Design	Country	Age	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 Nonusers	922 34,261	2019–2023/ retrospective	United States	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 Nonusers	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 Nonusers	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 h/NR	NR/NR
Stark 2022[12]	GLP-1 RA users Nonusers	59 118	2015–2020/ retrospective	United States	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 Nonusers	306 306	2018–2023/ retrospective	United States	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 h/ sedation	Dulaglutide 35% Semaglutide 36% Liraglutide 19% Other 14%/NR
Wu 2024[14]	GLP-1 RA users Nonusers	90 102	2019–2023 Retrospective	United States	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 h/ sedation 87% General anesthesia 13%	NR/329 (182–646) d

Table 1. Continued

Study	Arms	Sample Size	Study period/ Design	Country	Age	Male	Diabetes	Methodology	Definition of Retained Gastric Content/Duration of Fasting Before Endoscopy/ Sedation	GLP-1 RA Used/ Duration of Use
Meluban 2024[15,a]	GLP-1 RA users Nonusers	65 2045	2022–2023 Retrospective	United States	NR	NR	NR	Unadjusted analysis	Any solid content/ NR/NR	Semaglutide 60% Dulaglutide 26.1% Tirzepatide 4.6% Liraglutide 9.2%/ NR
Karlson 2024[16,a]	GLP-1 RA users Nonusers	579 281	2015–2023 Retrospective	United States	NR	NR	NR	Matching by age, diabetes, BMI, therapy	NR/NR/sedation	NR/NR
Gu 2024[17,a]	GLP-1 RA users Nonusers	152 152	2022–2023 Retrospective	United States	57.8 ± 11.8 57.2 ± 12.8	NR	NR	Propensity score matching	NR/NR/NR	Semaglutide 100%/4.7 ± 4 mo
Peng 2024[18,a]	GLP-1 RA users Nonusers	104 49	2023 Retrospective	United States	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 Nonusers	84 84	2017–2023 Retrospective	United States	53.9 ± 12.3 54 ± 11.8	71.4% 69%	86.9% 84.5%	Propensity score matching for confounders	POLPREP score/ median 10 h/ sedation 93.5% General anesthesia 6.5%	Dulaglutide 49% Semaglutide 24% Liraglutide 17% Others 10%/331 (132–535) days
Yeo 2024[20,b]	GLP-1 RA users Nonusers	3372 3331	2018–2020 Retrospective	United States	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[c] NR NR	NR/>6 mo
Barlowe 2024[21,b]	GLP-1 RA users Nonusers	15,119 21,664	2005–2021 Retrospective	United States	55 (49–60) 57 (52–61)	40% 48%	100% 100%	Propensity score weighting for age, sex, other comorbidities	NR[c] NR NR	NR/NR

Values are n, mean ± SD, or median (interquartile range).
BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; NR, not reported.
[a]Study published only as a conference abstract.
[b]Only patients undergoing upper endoscopy were included in the analysis.
[c]Not assessed as an outcome of this study.

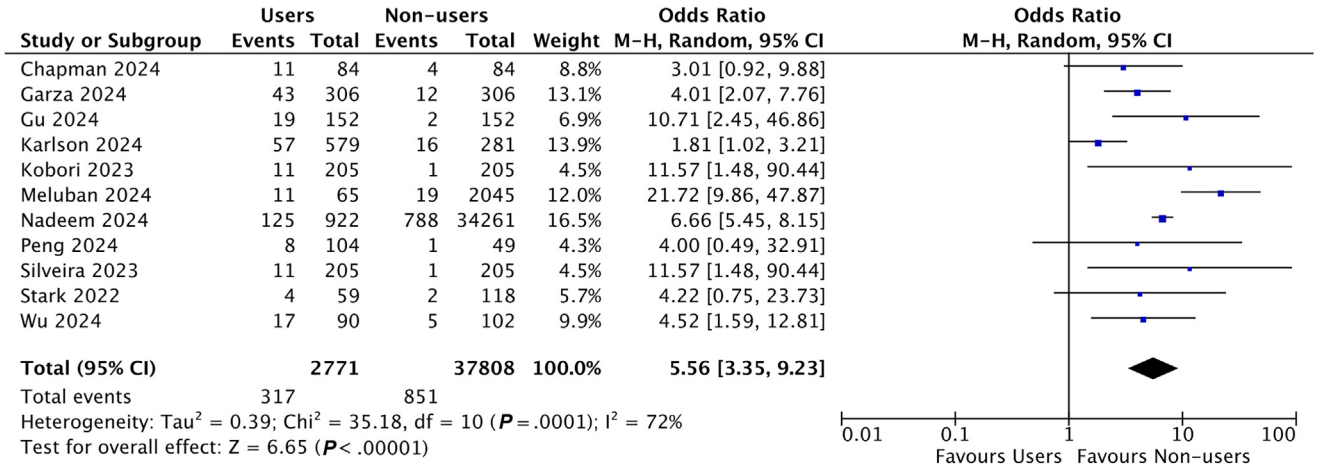

Figure 2. Forest plot comparing the rate of retained gastric content. The rate of retained gastric content was significantly higher in the group of patients using GLP-1 RA (odds ratio, 5.56; 95% confidence interval, 3.35–9.23; $P < .00001$), with high evidence of heterogeneity ($I^2 = 72\%$).

confirmed the higher rate of RGC in the group of GLP-1RA users (adjusted OR, 4.20; 95% CI, 3.42 to 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 1*A* and 1*B*.

Secondary Outcomes and Quality of Evidence

Five studies[9,12,16,18,19] with 1748 patients in the GLP-1RA group and 34,793 patients in the control group reported rates of aborted procedures. The pooled rate of aborted procedures was 1% (95% CI, 0.6% to 2%) in GLP-1RA users and 0.3% (95% CI, 0.2% to 0.4%) in nonusers. The meta-analysis showed this rate was significantly higher in the GLP-1RA group (OR, 5.13; 95% CI, 3.01 to 8.75), with no evidence of heterogeneity ($I^2 = 0\%$) (Supplementary Figure 2). The number needed to scope to observe 1 case of aborted procedure was 110 (95% CI, 50 to 400).

Three studies[9,12,18] with 1085 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% (95% CI, 1.5% to 3%) and 1% (95% CI, 0.8% to 1.3%) in the 2 groups, respectively. As shown in the Supplementary Figure 3, GLP-1RA users had a significantly higher need for repeated procedures (OR, 2.19; 95% CI, 1.43 to 3.35), with no heterogeneity ($I^2 = 0\%$). The number needed to scope for repeated procedures was 120 (95% CI, 50 to 600).

AEs were reported in 4 studies[9,10,13,14] with 1351 and 35,040 patients in the 2 groups, respectively. The pooled rate of AEs was 0.3% (95% CI, 0.001% to 0.7%) in GLP-1RA users and 0.1% (95% CI, 0.18% to 0.25%) in nonusers. As depicted in Supplementary Figure 4, there was no significant difference in terms of AE rate between the 2 groups (OR, 4.04; 95% CI, 0.63 to 26.03), with a nonsignificant moderate heterogeneity ($I^2 = 55\%$).

Six studies[9,10,13,14,20,21] with 19,842 GLP-1RA users and 60,035 nonusers reported rates of bronchial aspiration. Pooled rates of bronchial aspiration were 0.3% (95% CI, 0.001% to 0.1%) and 0.2% (95% CI, 0.001% to

Table 2. Overall and Sensitivity Analysis of the Retained Gastric Content Rate

Subgroup	Cohorts	Patients	OR (95% CI)	Within-Group Heterogeneity (I^2) (%)
Retained gastric content rate				
Overall	11	40,579	5.56 (3.35–9.23)	72
Full text papers	7	37,152	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 h	2	602	5.47 (2.16-13.87)	0
Fasting <12 h	3	1190	4.07 (2.33–7.09)	0
Adjusted OR	6	36,736	4.20 (3.42–5.15)	0

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 (<12 hours vs at least 12 hours), and pooling the adjusted OR.
CI, confidence interval; OR, odds ratio.

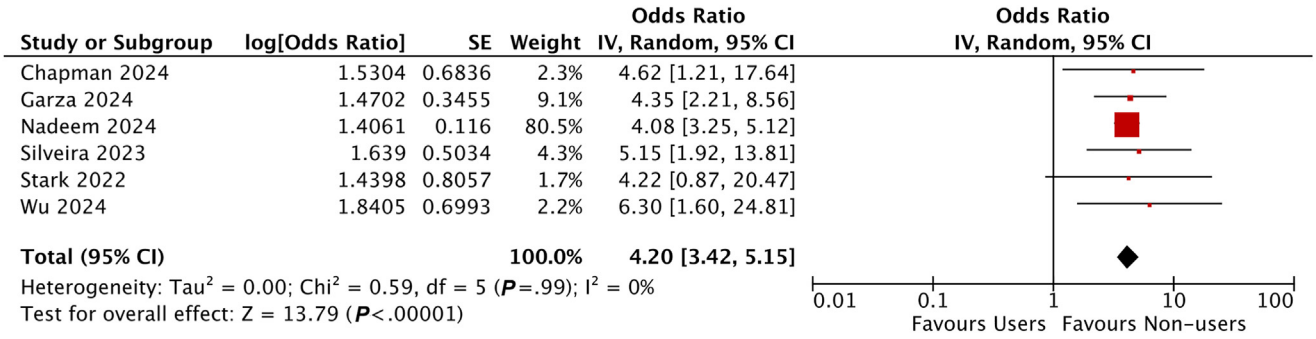

Figure 3. Forest plot pooling adjusted odds ratio for retained gastric content. Pooled adjusted odds ratio was 4.20 (95% confidence interval, 3.42–5.15; $P < .00001$) with no evidence of heterogeneity ($I^2 = 0\%$). Adjustment was for several variables including sex, age, BMI, diabetes, other therapies.

1%), respectively. As shown in Figure 4, there was no significant difference between the 2 groups (OR, 1.75; 95% CI, 0.64 to 4.77) with evidence of heterogeneity ($I^2 = 61\%$). The number needed to scope to observe 1 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 nonrandomized 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% CIs 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; 95% CI, 3.35 to 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 per 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

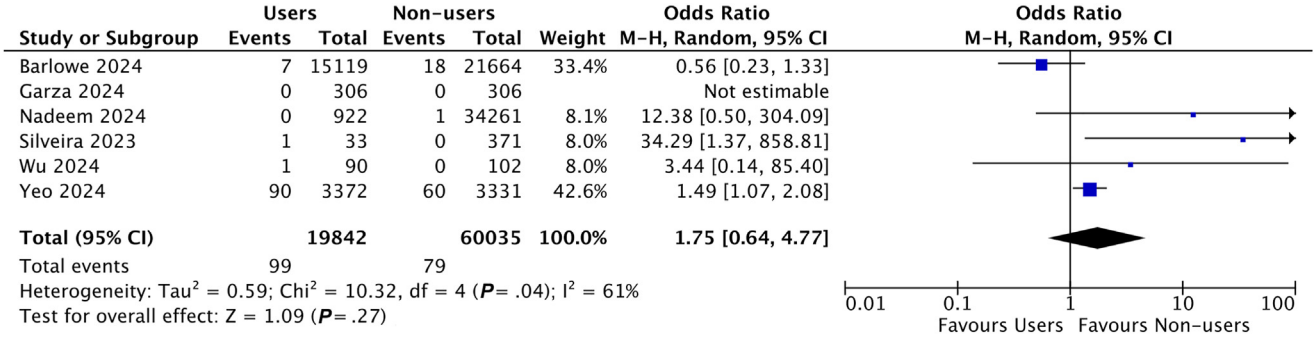

Figure 4. Forest plot comparing the aspiration rate in the 2 study groups. The rate of aspiration was not significantly different between the 2 groups (odds ratio, 1.75; 95% confidence interval, 0.64–4.77), with evidence of heterogeneity ($I^2 = 61\%$).

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-1RA use (withholding the drug in patients with diabetes could lead to more harm than benefits, whereas nondiabetic 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-1RA 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 or endoscopic ultrasound in which 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.

Second, 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 articles 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-1RA users. GLP-1RAs led to a significantly increased rate of aborted endoscopies (OR, 5.13; 95% CI, 3.01 to 8.75) and a higher need for repeat procedures (OR, 2.19; 95% CI, 1.43 to 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 for every 110 patients undergoing upper endoscopy while in GLP-1RA therapy would we observe an aborted procedure and only for every 120 patients would we 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 previous findings do not seem to be very impactful in clinical practice.

Fourth, the rates of RGCs, especially aspiration, did not seem to show a statistically significant difference between the 2 groups, but rather only a possible increase (OR, 4.04; 95% CI, 0.63 to 26.03; and OR, 1.75; 95% CI, 0.64 to 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 call for a note of caution in this regard and prevent 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-1RAs 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-1RA 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 GLP-1RA use is not associated with increased risk of pulmonary complications after upper endoscopy compared with 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 4134 upper endoscopic procedures conducted in GLP-1RA 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 2 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 randomized controlled trials, are needed to draw definitive conclusions on this topic.

Our study has limitations. First, 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. Second, 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. Third, 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 United States, 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 2 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 AEs, particularly aspiration, is low and not significantly different between the 2 groups. Hence, prolonging the duration of fasting for solids could represent the optimal approach in these patients, although this strategy requires further evaluation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2024.07.021.

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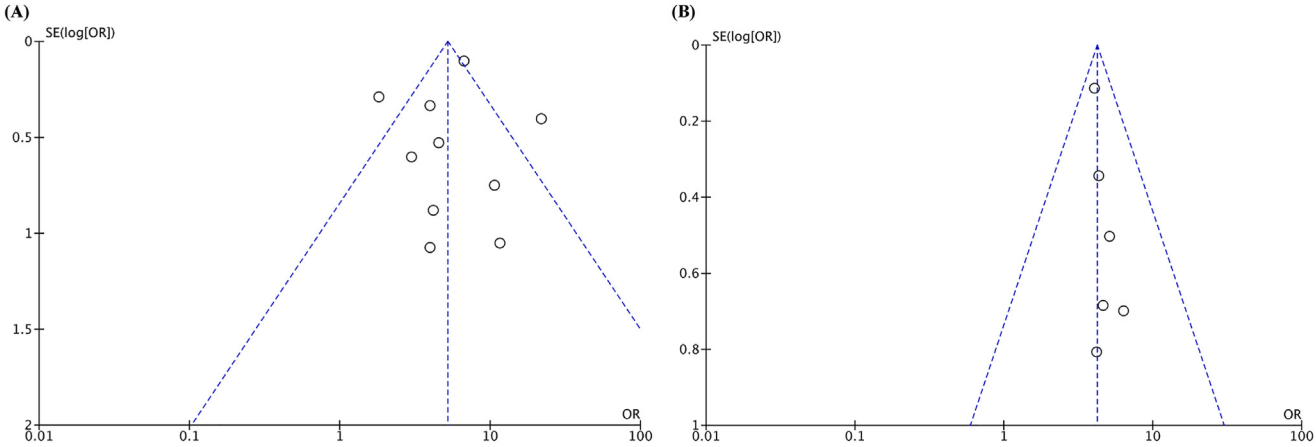
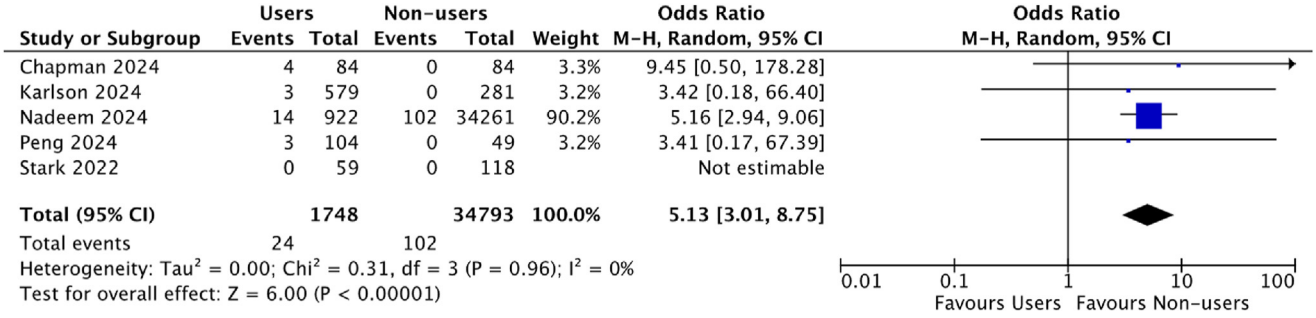
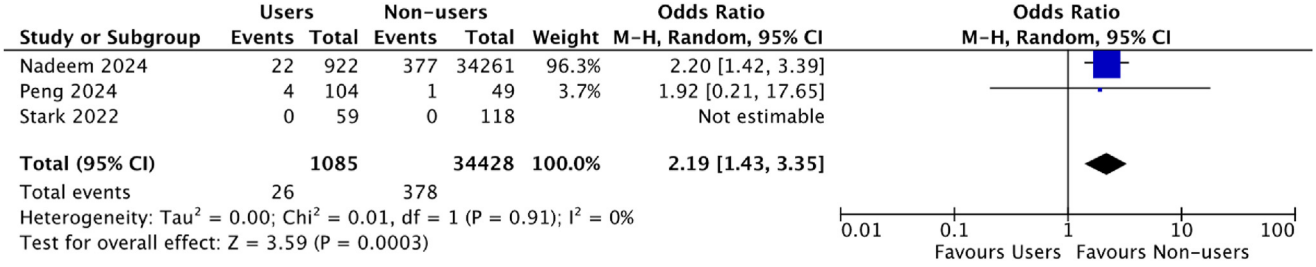
Conflicts of Interest
The authors disclose no conflicts.



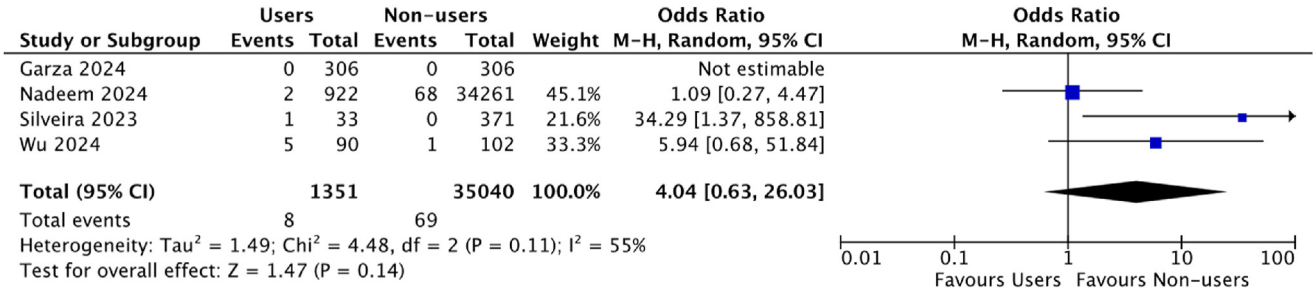
Supplementary Figure 1. Funnel plot for (*A*) retained gastric content rate and (*B*) adjusted odds ratio (OR).



Supplementary Figure 2. Forest plot for rate of aborted procedures. CI, confidence interval; M-H, Mantel-Haenszel.



Supplementary Figure 3. Forest plot for rate of repeated procedures. CI, confidence interval; M-H, Mantel-Haenszel.



Supplementary Figure 4. Forest plot for adverse event rate. CI, confidence interval; M-H, Mantel-Haenszel.

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

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

Supplementary Table 2. Table of Evidence

			Certainty Assessment							
Outcome	Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Effect Estimate	Certainty	Comments
Retained gastric content	11	Observational	High	High	High	Low	Low	OR 5.56 (95% CI, 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 (95% CI, 3.42-5.15)	◯◯◯◯ Very low	Based on nonrandomized studies, high indirectness due to different regimens of fasting before endoscopy
Aborted procedures	5	Observational Studies	High	Low	High	High	Low	OR 5.13 (95% CI, 3.01-8.75)	◯◯◯◯ Very low	Based on nonrandomized 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 (95% CI, 1.43-3.35)	◯◯◯◯ Very low	Based on nonrandomized 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 (95% CI, 0.63-26.03)	◯◯◯◯ Very low	Based on nonrandomized studies, high imprecision due to wide CIs, high heterogeneity
Aspiration	6	Observational studies	High	High	High	High	Low	OR 1.75 (95% CI, 0.64-4.77)	◯◯◯◯ Very low	Based on nonrandomized studies, high imprecision due to wide CIs, high heterogeneity

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.