Critical Care Explorations
May 2025 • Volume 7 • Number 5 • e1263

OBSERVATIONAL STUDY

OPEN

Impact of Glucagon-Like Peptide-1 Receptor Agonist Exposure on Gastrointestinal Outcomes Among ICU Patients: A Multicenter Matched Cohort Study

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IMPORTANCE: Patients admitted to the ICU often experience gastrointestinal complications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become increasingly prevalent in the treatment of type 2 diabetes mellitus and obesity, and there is evidence that their use may be associated with an increased risk of clinically significant gastrointestinal events. However, their impact on critically ill patients admitted to the medical ICU is unknown.

OBJECTIVES: This study examined whether pre-ICU use of GLP-1RAs was associated with increased incidence of gastrointestinal complications and hospitalization outcomes.

DESIGN, SETTING AND PARTICIPANTS: Multicenter, retrospective cohort study of critically ill patients admitted to academic and community hospitals of Mayo Clinic Health System from January 1, 2018, to December 31, 2023. Patients who were admitted to surgical ICUs and those who were exposed to GLP-1RA medications before but did not have an active prescription within 30 days of admission were excluded. Patients exposed to GLP-1RA were matched with those nonexposed in a 1:1 fashion based on demographic factors, factors affecting gastrointestinal motility, overall illness burden, and clinical acuity.

MAIN OUTCOMES AND MEASURES: Outcomes of interest were the development of gastrointestinal dysfunction, ICU- and hospital-free days, and mortality.

RESULTS: A total of 31,327 patients with diabetes or obesity were identified of whom these, 631 were exposed to GLP-1RA before admission. In the matched cohort of 1262 patients, baseline variables were evenly distributed between the two groups. There were no significant differences in the odds of developing nausea/vomiting, constipation, ileus, obstruction, impaction, or aspiration pneumonia between the GLP-1RA exposed and unexposed groups. Similarly, ICU and hospital mortality rates were comparable across the two groups. However, GLP-1RA exposed patients had significantly more hospital-free days compared with unexposed patients (estimate, 1.19; 95% CI, 0.38–2.0; $p = 0.004$).

CONCLUSIONS AND RELEVANCE: GLP-1RA exposure was not associated with increased odds of clinically significant gastrointestinal complications in nonsurgical critically ill patients. Increased hospital-free days observed among GLP-1RA exposed patients requires further study.

KEYWORDS: critical care; gastrointestinal motility; gastrointestinal tract; gastrointestinal transit; glucagon-like peptide-1 receptor agonist

DOI: 10.1097/CCE.0000000000001263

KEY POINTS

Question: Does pre-ICU use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) increase the incidence of clinically significant gastrointestinal events?

Findings: Of 31,327 patients with diabetes or obesity, 631 GLP-1RA exposed patients were identified. GLP-1RA exposure was found to be associated with increased odds of impaction (adjusted odds ratio, 2.34; 95% CI, 1.19–4.58) as well as hospital-free days (estimate, 1.00; 95% CI, 0.37–1.63). After GLP-1RA patients were matched for factors impacting gastrointestinal motility, only the association with hospital-free days remained clinically significant (estimate, 1.19; 95% CI, 0.38–2.0; $p = 0.004$; exp[β], 1.16; 95% CI, 1.04–1.28).

Meaning: Among patients admitted to the medical ICU, GLP-1RA exposure may not be associated with adverse gastrointestinal outcomes or exacerbate gastrointestinal dysfunction.

Gastrointestinal dysfunction is a common complication of critical illness with profound implications for patient outcomes. Up to 60% of patients in the ICU experience gastrointestinal dysfunction, which can manifest as nausea, vomiting, constipation, aspiration, ileus, and small bowel obstruction (1–3). The pathophysiology behind these derangements is believed to be multifactorial and involves disruptions to both the neural and hormonal regulation of the gastrointestinal tract in the setting of shock states, excess catecholamine release, and medication administrations (4–6). Often, initiation of enteral nutrition is delayed in affected patients, leading to degradation of gut epithelial integrity and translocation of pathogenic organisms (7). This can exacerbate the systemic immune response and trigger worsening multisystem organ dysfunction, increasing morbidity, mortality, length of stay, and overall cost of care (8–10).

Since their approval to treat type 2 diabetes mellitus (T2DM) in 2005 and obesity in 2014, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become increasingly prevalent. The annual prevalence of GLP-1RA prescriptions has increased from 0.5% in 2020 to 3% in 2023, with up to 12% of adults reporting use of a GLP-1RA (11, 12). GLP-1RAs primarily exert their anti-hyperglycemic effects through enhancement of the incretin effect by stimulating beta cells, enhancing glucagon secretion, and promoting beta-cell proliferation (13). Aside from affecting pancreatic tissues, receptors for GLP-1RAs are widely distributed throughout the gastrointestinal tract including the gastric corpus, gastric antrum, duodenum, jejunum, ileum, and cecum with varying levels of expression (14). Stimulation of these receptors leads to the well-known motility effects of GLP-1RAs through inhibition of antro-duodenal motility, stimulus of pyloric motility, and reduction of the number of migrating motor complexes (15). While there are minor differences between commercially available agents, all formulations of GLP-1RAs significantly delay gastric emptying (16). As a consequence of their mechanism of action, GLP-1RA use is associated with multiple gastrointestinal side effects such as nausea and vomiting (23.4%), constipation (30.4%), abdominal pain (57.6%), and gastroparesis (5.1%) (17–22).

Recent case reports have highlighted the potential for GLP-1RA exposure to lead to significant adverse effects in susceptible patient populations, with implications for clinical practice. Specifically, reports have documented intractable nausea/vomiting (23), retained gastric contents (24), and aspiration events (25) complicating general anesthesia and endoscopic procedures. Recently published multisociety clinical practice guidelines regarding the perioperative use of GLP-1RAs reflect these known risks, recommending stratification of patients on GLP-1RAs and withholding medications in high-risk individuals in the perioperative setting (26).

Given the propensity for patients requiring ICU level care to develop gastrointestinal dysfunction, we hypothesized that use of GLP-1RAs before ICU admission might contribute to a higher incidence of clinically significant gastrointestinal outcomes. We therefore conducted a retrospective cohort study of patients who had obesity or diabetes mellitus (DM) and were admitted to ICU to examine the relationship between GLP-1RA use and the incidence of nausea/vomiting, constipation, ileus, obstruction, impaction, aspiration pneumonia, or gastroparesis, as well as hospital and ICU length of stay and mortality.

METHODOLOGY

The study protocol was reviewed and approved on January 29, 2024, by the Mayo Clinic institutional review board (No. 23-013232: Retrospective review of the impact of glucagon-like peptide 1 agonists on gastrointestinal motility and outcomes in a medical intensive care unit). All research endeavors were in accordance with the ethical standards of the institutional review board and with the Helsinki Declaration of 1975.

Design, Setting, and Participants

This was a retrospective, matched cohort study evaluating the association of prehospital GLP-1RA exposure with gastrointestinal complications in patients admitted to the ICU. All consecutive adult patients presenting to a Mayo Clinic ICU (Rochester, MN; Scottsdale, AZ; Jacksonville, FL; Mayo Clinic Health Systems: MN and WI) from January 1, 2018, to December 31, 2023, were evaluated for inclusion. Patients were excluded if their ICU length of stay was less than 24 hours, they were admitted to a surgical ICU, they did not have a signed Minnesota research authorization form on file, or they did not have diabetes or obesity. Only the patient's index admission during the study timeframe was considered in the final analysis. Additionally, patients who were exposed to GLP-1RA medications but did not have an active prescription within 30 days of admission were excluded as their exposure status could not be reliably determined.

Variable Definitions

We identified GLP-1RA exposure as having an active, outpatient prescription for one of the commercially available GLP-1RAs (exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide, albiglutide, or tirzepatide) within 30 days of index admission (**eTable 1**, https://links.lww.com/CCX/B508) (20). Medication exposure information was retrieved using the epic electronic medical records system Slicer-Dicer tool (Epic Systems Corporation, Verona, WI) (27) with the guidance of a pharmacist researcher (Z.R.). We evaluated the reliability of electronically retrieved exposure information through manual chart review (conducted by C.G.G., M.N.) of a random sample of 58 records without access to the result of the electronic abstraction (eight patients exposed to GLP-1RA, 50 without GLP-1RA exposure). The agreement was 98.3% (8/8 exposed patients, 49/58 for unexposed patients), with a kappa of 93%.

Each GLP-1RA exposed patient was subsequently matched to one control based on the following factors: age at the time of ICU admission (± 3 yr), sex, body mass index (BMI) (± 0.5 kg/m^2), smoking status, presence of obesity (determined via BMI ≥ 30 kg/m^2 [28]), DM (determined by *International Classification of Diseases*, 10th Edition [ICD-10] codes), motility altering prescription drugs (**eTable 2**, https://links.lww.com/CCX/B508), comorbidities associated with decreased motility (**eTable 3**, https://links.lww.com/CCX/B508), history of abdominal surgeries (eTable 3, https://links.lww.com/CCX/B508), any surgery within 48 hours of ICU admission, Charlson Comorbidity Index (CCI, categorized as groups of 0, 1–2, 3–4, and ≥ 5) (29, 30), and Acute Physiology and Chronic Health Evaluation (APACHE)-III score (± 1 U).

Outcomes

The primary outcome of our study was the incidence of gastrointestinal complications, specifically nausea/vomiting, constipation, ileus, obstruction, impaction, and aspiration pneumonia among GLP-1RA exposed and nonexposed individuals. These were assessed via ICD-10 codes (**eTable 4**, https://links.lww.com/CCX/B508) assigned during the admission period of interest. ICU-free days and hospital-free days (calculated as the number of days alive and out of the hospital or ICU within 28 d of admission, with a score of 0 for those who died during the stay or were hospitalized for longer than 28 d) (31), ICU mortality, and hospital mortality were also assessed between the groups as secondary outcomes.

Statistical Analysis

Sample size calculations and power analyses were not performed as all eligible patients in the specified timeframe were included (**Fig. 1**). Summary statistics were reported as counts and percentages or medians with interquartile ranges (IQRs) according to variable types. The post-match balance was evaluated via standardized mean differences (**Fig. 2**). Comparative analyses in the matched cohort were performed using conditional logistic regression and

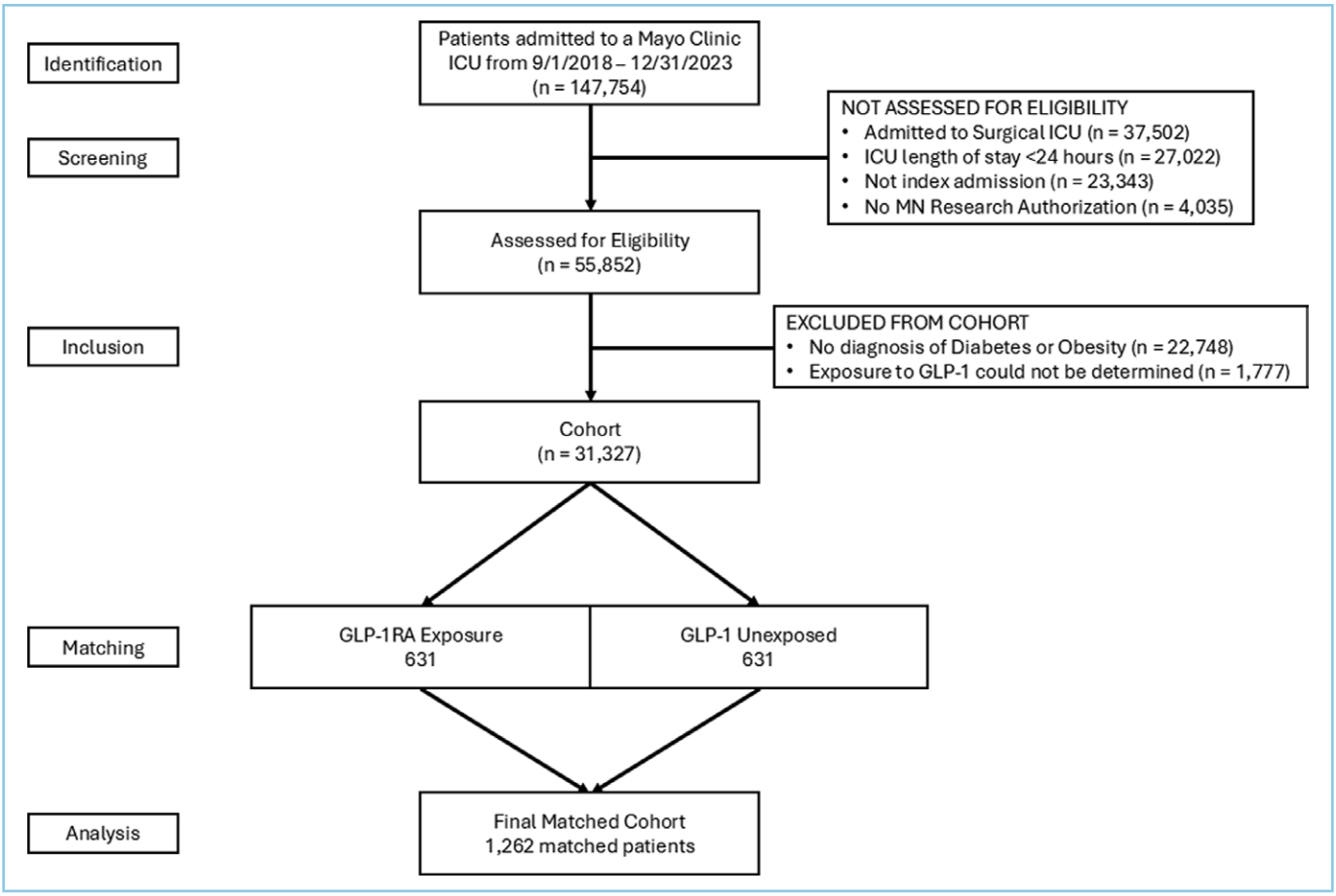

Figure 1. Strengthening the Reporting of Observational Studies in Epidemiology diagram. GLP-1RA = glucagon-like peptide-1 receptor agonist, MN = Minnesota.

mixed linear models and comparisons in the entire cohort were performed via chi-square test and Mann-Whitney *U* test alongside logistic and linear regression for multivariable models. The results were reported as odds ratios (ORs), estimates, 95% CIs, and *p* values. To facilitate comparison with ORs reported for categorical outcomes, we also exponentiated the estimate from the linear mixed-effects model, providing a relative effect interpretation consistent with our statistical approach. Additional sensitivity analyses were performed before matching (adjusted for BMI, APACHE-III score, age, and CCI). Subgroup analysis was performed to evaluate the effect of individual GLP-1RAs, the presence or absence of diabetes, surgery within 48 hours, and initiation of GLP-1RA within 30 days of admission on gastrointestinal outcomes.

Matching was performed as nearest neighbor matching without replacement using Mahalanobis distance for multivariate matching by MatchIt package of R (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/). The statistical analysis was conducted using IBM SPSS v27.0 (Statistical Package for Social Sciences; IBM Corp, Armonk, NY) and R v4.4.1 (R Foundation for Statistical Computing) statistical software programs. A two-sided *p* value of less than 0.05 was considered statistically significant. Figures were created using Microsoft Power Point (Microsoft Corporation, Redmond, WA) and GraphPad Prism (GraphPad Software, Boston, MA).

RESULTS

A total of 147,754 patients were identified as admitted to one of the ICUs during the study timeframe, of which 116,427 were excluded (see Strengthening the Reporting of Observational Studies in Epidemiology flowchart, Fig. 1). Of the 31,327 eligible patients (**eTable 5**, https://links.lww.com/CCX/B508, describing the baseline characteristics of the unmatched cohort), 631 had been exposed to GLP-1RAs before ICU

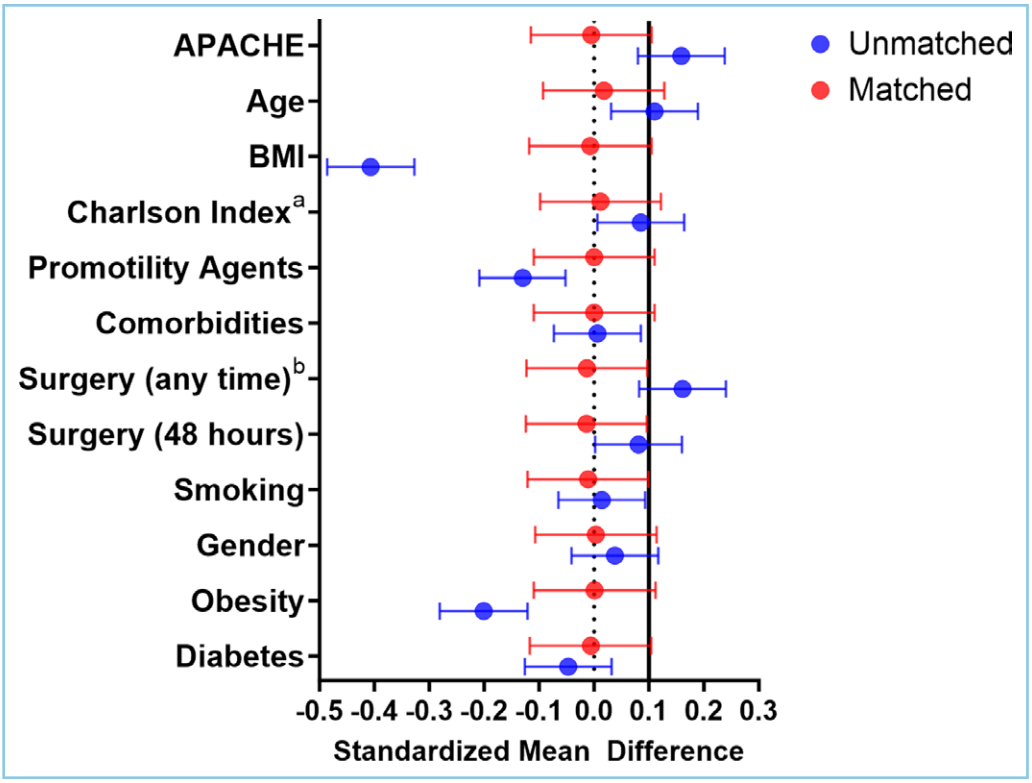

Figure 2. Standardized mean differences (SMDs) of cohort characteristics before and after matching. Characteristics were considered well matched if the SMD was less than or equal to 0.1. [a]Charlson Comorbidity Index was entered into the match by groups (0, 1–2, 3–4, ≥ 5). [b]Only abdominal surgeries were considered. APACHE = Acute Physiology and Chronic Health Evaluation, BMI = body mass index.

admission. These were subsequently matched to one control each for a final cohort of 1262 patients.

Table 1 details the demographics, factors affecting gastrointestinal motility, and overall illness burden and clinical acuity of the matched cohort. Most patients were male (56.2%), the median age was 65 years (IQR, 56–72 yr), and the median BMI was 35.0 kg/m^2 (IQR, 30.0–41.4 kg/m^2). Most patients either had a diagnosis of obesity (74.1%) or diabetes (93.6%), and 30.0% used insulin. The median CCI was 2 (IQR, 1–3). At the time of admission, the average APACHE-III score was 64 (IQR, 46–91). Regarding surgical history of the cohort, 15.6% of the patients had abdominal surgery in their lifetime and 27.7% had surgery within 48 hours of admission. There were no significant differences noted between GLP-1RA exposed and unexposed individuals with regards to any of the baseline variables of interest after the matching process (Fig. 2).

In the uncontrolled analysis of the unmatched cohort (**eTable 6**, https://links.lww.com/CCX/B508), GLP-1RA exposure was associated with decreased odds of obstruction (OR, 0.41; 95% CI, 0.18–0.91; p = 0.024). Both ICU mortality and in-hospital mortality were unaffected by GLP-1RA use, and after controlling for age, BMI, APACHE-III score, and CCI, only impaction and hospital-free days were found to be statistically significantly different between the two groups (OR, 2.34; 95% CI, 1.19–4.58; p = 0.014; estimate, 1.00; 95% CI, 0.37–1.63; p = 0.002). After the matching process, only the number of hospital-free days remained significantly different between GLP-1RA exposed and unexposed patients (estimate, 1.19; 95% CI, 0.38–2.0; p = 0.004; exp[β], 1.16; 95% CI, 1.04–1.28) (**Table 2**).

Several subgroup analyses were undertaken. GLP-1RA exposure was not associated with gastrointestinal complications, ICU/hospital mortality, or ICU/hospital-free days in subgroups of patients who underwent surgery within 48 hours of admission and those who did not (**eTable 7**, https://links.lww.com/CCX/B508). In those with diabetes, the use of a GLP-1RA was associated with increased hospital-free days (estimate, 1.2; 95% CI, 0.36–2.03; p = 0.005; exp[β], 1.15; 95% CI, 1.03–1.28) (**eTable 8**, https://links.lww.com/CCX/B508). The effect of various GLP-1RA formulations was also examined (**Table 3**). Most GLP-1RA scripts were for dulaglutide (n = 244) followed by semaglutide (n = 241). The only statistically significant finding was decreased ICU mortality among those exposed to dulaglutide (OR, 0.25; 95% CI, 0.07–0.89; p = 0.032). Finally, initiation of a GLP-1RA within 30 days of admission to the ICU was associated with significantly higher number of ICU-free days (estimate, 2.05; 95% CI, 0.33–3.78; p = 0.021) but had no other impact on either the primary or secondary outcomes (**Table 4**).

TABLE 1.
Demographics, Factors Affecting Gastrointestinal Motility, and Overall Clinical Acuity of Matched Cohort

Variables, *n* = No. of Patients With Available Data	Total Patients (*n* = 1262)	GLP-1RA Exposed (*n* = 631)	GLP-1RA Unexposed (*n* = 631)	*p*
Age[a], median (IQR)	65 (56–72)	65 (56–72)	64 (57–72)	0.122
Gender female[a], *n* (%)	553 (43.8)	277 (43.9)	276 (43.7)	0.657
Body mass index[a], median (IQR)	35.0 (30.0–41.4)	34.5 (29.7–41.4)	34.5 (29.7–41.5)	0.311
Obesity, *n* (%), *n* = 1239[b]	918 (74.1)	457 (74.1)	461 (74.1)	0.999
Diabetes[a], *n* (%)	1181 (93.6)	591 (93.7)	590 (93.5)	0.999
Hemoglobin A1c, median (IQR)	7.10 (6.10–8.60)	7.50 (6.50–9.10)	6.60 (5.80–7.80)	< 0.001
Insulin, *n* (%)	378 (30.0)	282 (44.7)	96 (15.2)	< 0.001
Charlson Comorbidity Index, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.146
Charlson Comorbidity Index, grouped[a], *n* (%)				NA[e]
0	139 (11.0)	72 (11.4)	67 (10.6)	
1–2	703 (55.7)	349 (55.3)	354 (56.1)	
3–4	404 (32.0)	202 (32)	202 (32)	
≥ 5	16 (1.3)	8 (1.3)	8 (1.3)	
Acute Physiology and Chronic Health Evaluation III score[a], median (IQR), *n* = 1261[b]	64 (46–91)	63 (46–92)	64 (46–90)	0.416
Comorbidities affecting motility[a,c], *n* (%)	12 (1.0)	6 (1)	6 (1)	NA[e]
Promotility agents[a,d], *n* (%)	1206 (95.6)	603 (95.6)	603 (95.6)	NA[e]
Abdominal surgery[a], *n* (%)	197 (15.6)	100 (15.8)	97 (15.4)	0.999
Surgery within 48 hr[a], *n* (%)	350 (27.7)	177 (28.1)	173 (27.4)	0.142
Location, *n* (%)				0.071
Mayo Clinic Arizona	94 (7.4)	38 (6.0)	56 (8.9)	
Mayo Clinic Florida	452 (35.8)	233 (36.9)	219 (34.7)	
Mayo Clinic Health Systems	417 (33.0)	219 (34.7)	198 (31.4)	
Mayo Clinic Rochester	299 (23.7)	141 (22.3)	158 (25.0)	

GLP-1RA = glucagon-like peptide-1 receptor agonist, IQR = interquartile range, NA = not applicable.
[a]Variables included in matching.
[b]The count of patients with available data for variables with missing values. If no subject count is specified, it indicates there were no missing values.
[c]See eTable 3 (https://links.lww.com/CCX/B508).
[d]See eTable 2 (https://links.lww.com/CCX/B508).
[e]*p* values not calculated.

DISCUSSION

In this retrospective, matched cohort study of patients admitted to a medical ICU, GLP-1RA exposure was not associated with increased odds of clinically significant gastrointestinal complications such as nausea/vomiting, obstruction, impaction, or aspiration pneumonia. On the contrary, exposure to GLP-1RAs was associated with increased hospital-free days, suggesting potential benefits. While GLP-1RA exposure did not significantly impact ICU-free days or ICU mortality, its association

TABLE 2.
Univariate Analysis of the Matched Cohort

Outcomes	GLP-1RA Exposed (*n* = 631)	GLP-1RA Unexposed (*n* = 631)	OR (95% CI); *p*
Aspiration, *n* (%)	48 (7.6)	55 (8.7)	0.84 (0.55–1.3); 0.443
Constipation, *n* (%)	66 (10.5)	60 (9.5)	1.11 (0.77–1.6); 0.578
Hospital mortality, *n* (%)	37 (5.9)	43 (6.8)	0.83 (0.5–1.36); 0.447
ICU mortality, *n* (%)	20 (3.2)	27 (4.3)	0.7 (0.37–1.32); 0.265
Ileus, *n* (%)	5 (0.8)	3 (0.5)	1.67 (0.4–6.97); 0.484
Impaction, *n* (%)	9 (1.4)	6 (1.0)	1.6 (0.52–4.89); 0.41
Nausea and/or vomiting, *n* (%)	74 (11.7)	60 (9.5)	1.27 (0.88–1.84); 0.195
Obstruction, *n* (%)	6 (1.0)	14 (2.2)	0.43 (0.16–1.12); 0.083
			Estimate (95% CI); *p*
Hospital-free days, median (IQR)	22.0 (17.9–24.5)	21.7 (14.7–24.3)	1.19 (0.38–2.0); 0.004
ICU-free days, median (IQR)	25.5 (23.4–26.3)	25.6 (23.2–26.4)	0.22 (–0.38 to 0.82); 0.723

GLP-1RA = glucagon-like peptide-1 receptor agonist, IQR = interquartile range, OR = odds ratio.

with shorter hospital stays warrants further exploration into its potential protective effects.

Mechanistically, critical illness is thought to disrupt regulatory hormones such as ghrelin, motilin, cholecystokinin, GLP1/GLP2, and PYY as well as physiologic peristaltic wave generation (32). Given the class effects of GLP-1RAs such as delayed gastric emptying and decreased small bowel transit time, we hypothesized that their use could potentiate the effects of critical illness (17). In an initial unmatched analysis, pre-ICU GLP-1RA exposure was associated with increased odds of impaction; however, this association was not observed after adjusting for comorbidities, pharmacological agents affecting gastrointestinal motility, surgical history, and illness severity. While there have been no comparable studies conducted in the ICU, recent retrospective reviews have shown that concerns regarding GLP-1RA effects on gastrointestinal complications may have been overstated both in the perioperative setting (33, 34) and during endoscopic procedures (35, 36). This is supported by a review of GLP-1RA overdose cases reported to the U.S. Poison Control Center, which found that most adverse effects were mild in severity, consisting of nausea and vomiting, and rarely required admission to the hospital for management (37). While enteral nutrition is often delayed upon admission to the medical ICU, multiple professional societies support early initiation of nutrition including the American College of Gastroenterology, the American Society for Parenteral and Enteral Nutrition, and the 2021 Surviving Sepsis Campaign guidelines (38–40). Our findings suggest that a history of GLP-1RA use may not necessitate delaying early enteral nutrition, and adherence to major guidelines could be reasonable in this context.

Our analysis also highlighted a compelling association between increased hospital-free days and GLP-1RA exposure. These findings are similar to a study published by Heo et al (41) examining patients with T2DM who were admitted after undergoing total hip arthroplasty, which found that prehospital GLP-1RA exposure was associated with a lower probability of prolonged hospitalization. There are several possible explanations for these findings. First, GLP-1RA use may contribute to better prehospital glycemic control, thereby improving hospital outcomes. A review of GLP-1RA trial data shows that up to 80% of patients achieved a target A1c of less than 7% on a GLP-1RA (42). Among patients admitted to the ICU, inadequate prehospital glycemic control has been associated with increased incidence of moderate and severe hypoglycemia and subsequent mortality (17). Aside from better glycemic control, GLP-1RAs might contribute to decreased hospital length of stay through widespread pleiotropic effects. GLP-1RA use has been associated

TABLE 3.
Sensitivity Analysis of Individual Glucagon-Like Peptide-1 Receptor Agonists

	Dulaglutide, *n* = 224 Pairs	Exenatide, *n* = 24 Pairs	Liraglutide, *n* = 118 Pairs	Lixisenatide, *n* = 10 Pairs	Semaglutide, *n* = 241 Pairs	Tirzepatide, *n* = 12 Pairs
Outcomes	**OR (95% CI); *p***	**OR (95% CI); *p***	**OR (95% CI); *p***	**OR (95% CI); *p***	**OR (95% CI); *p***	**OR (95% CI); *p***
Aspiration	0.89 (0.45–1.74); 0.731	0.5 (0.05–5.51); 0.571	1 (0.35–2.85); 1	Ing[a]; 0.999	0.75 (0.35–1.59); 0.451	0.5 (0.05–5.14); 0.571
Constipation	1.52 (0.88–2.64); 0.134	0.25 (0.03–2.24); 0.215	1.22 (0.51–2.95); 0.655	Inf[a]; 0.999	0.75 (0.38–1.46); 0.400	Inf[a]; 0.999
Hospital mortality	0.67 (0.3–1.48); 0.320	Inf[a]; 0.999	1.29 (0.48–3.45); 0.618	NA[a]	0.82 (0.34–1.97); 0.655	NA[a]
ICU mortality	0.25 (0.07–0.89); 0.032	1 (0.06–15.99); 1	1.25 (0.34–4.65); 0.739	NA[a]	1.17 (0.39–3.47); 0.782	NA[a]
Ileus	3 (0.31–28.84); 0.341	NA[a]	Inf[a]; 0.999	NA[a]	Inf[a]; 0.999	NA[a]
Impaction	0.67 (0.11–3.99); 0.667	NA[a]	1 (0.14–7.1); 1	NA[a]	Inf[a]; 0.999	NA[a]
Nausea and/or vomiting	1.19 (0.61–2.31); 0.612	1 (0.14–7.1); 1	2.17 (0.82–5.7); 0.117	Inf[a]; 0.999	1.12 (0.65–1.92); 0.680	3 (0.31–28.84); 0.341
Obstruction	0.5 (0.09–2.73); 0.423	Inf[a]; 0.999	0.25 (0.03–2.24); 0.215	NA[a]	0.6 (0.14–2.51); 0.484	NA[a]
	Estimate (95% CI); *p*	**Estimate (95% CI); *p***	**Estimate (95% CI); *p***	**Estimate (95% CI); *p***	**Estimate (95% CI); *p***	**Estimate (95% CI); *p***
Hospital-free days	1.22 (–0.17 to 2.6); 0.086	1.01 (–2.26 to 4.27); 0.543	1.13 (–1.01 to 3.27); 0.299	1.23 (–4.28 to 6.74); 0.661	1.18 (–0.07 to 2.42); 0.064	2.21 (–2.39 to 6.81); 0.349
ICU-free days	0.87 (–0.11 to 1.85); 0.084	0.84 (–2.56 to 4.23); 0.632	–0.03 (–1.54 to 1.47); 0.968	2.44 (–1.74 to 6.62); 0.277	–0.46 (–1.42 to 0.51); 0.353	1.67 (–2.69 to 6.04); 0.461

Inf = infinity, NA = not applicable, OR = odds ratio.

[a]Could not be calculated due to the number of events or their distribution patterns.

TABLE 4.
Sensitivity Analysis—Initiation of Glucagon-Like Peptide-1 Receptor Agonist Within 30 Days of ICU Admission

Outcomes, *n* = No. of Patients	GLP-1RA Exposed (*n* = 168)	GLP-1RA Unexposed (*n* = 168)	OR (95% CI); *p*
Aspiration, *n* (%)	12 (12.6)	10 (10.5)	1.25 (0.49–3.17); 0.638
Constipation, *n* (%)	18 (18.9)	12 (12.6)	1.6 (0.73–3.53); 0.244
Hospital mortality, *n* (%)	7 (7.4)	8 (8.4)	0.86 (0.29–2.55); 0.782
ICU mortality, *n* (%)	2 (2.1)	6 (6.3)	0.33 (0.07–1.65); 0.178
Ileus, *n* (%)	1 (1.1)	0 (0.0)	NA[a]; 0.999
Impaction, *n* (%)	1 (1.1)	2 (2.1)	0.5 (0.45–5.51); 0.571
Nausea and/or vomiting, *n* (%)	12 (12.6)	7 (7.4)	1.71 (0.67–4.35); 0.257
Obstruction, *n* (%)	1 (1.1)	0 (0.0)	NA[a]; 0.999
			Estimate (95% CI); *p*
Hospital-free days, median (IQR)	20.73 (15.07–23.72)	19.75 (8.91–23.56)	1.98 (–0.23 to 4.19); 0.08
ICU-free days, median (IQR)	25.83 (23.84–26.47)	25.39 (21.87–26.30)	2.05 (0.33–3.78); 0.021

GLP-1RA = glucagon-like peptide-1 receptor agonist, IQR = interquartile range, NA = not applicable, OR = odds ratio.
[a]Could not be calculated due to the number of events or their distribution patterns.

with decreased major adverse cardiovascular events, heart failure exacerbations, lower rates of kidney disease, improvement in blood pressure, and reduction of lipemia and inflammation (43–45). Finally, GLP-1RA use may be a proxy for socioeconomic status. Higher median household income (> $50,000/yr) is associated with higher GLP-1RA use (46). Socioeconomic status has been implicated in playing a role in hospital length of stay, with possible mechanisms including increasing ease in arranging for post-hospital accommodations and transportation (47, 48).

We performed several subgroup and sensitivity analyses examining factors that may contribute to heightened GLP-1RA effects such as recent initiation (43–45), the presence of diabetes (46), stratification by GLP-1RA class (49), and initiation within 30 days of admission and noted no significant associations between GLP-1RAs and gastrointestinal complications. With respect to secondary outcomes, GLP-1RA use was associated with increased hospital-free days in patients with diabetes and increased ICU-free days among those who initiated the drug within 30 days of admission. We also note that the use of dulaglutide was associated with decreased ICU mortality. Given the small sample sizes of many measured outcomes, the interpretation of these findings is limited.

Our study has several strengths. First, the data available to our investigative team came from a diverse array of geographical locations, practice environments, and patient populations, increasing the generalizability of our findings. Analysis regarding the distribution of GLP-1 use (Table 1) shows that it was equal across geographic locations as well as between academic and nonacademic centers. Second, we were able to reliably determine pre-ICU GLP-1RA exposure as confirmed by our calculated Kappa of 93%, strengthening the impact of our findings. Third, our study controlled for numerous factors that could confound measurement of gastrointestinal motility during the matching process.

There are several limitations to our study. First, outcomes were determined based upon ICD-10 codes. These are usually not entered by the treating clinician and therefore may not fully capture the extent of specific gastrointestinal symptoms the patient is experiencing. Second, determination of GLP-1RA exposure may have missed or mischaracterized patients. This was an automated process based off assessment of outpatient prescriptions. To help mitigate this limitation, we conducted manual chart reviews to confirm reliability, indicating excellent agreement (98.3%, with a kappa of 93%). It is important to note that the presence of an active

prescription does not necessarily confirm that the medication was dispensed, that the patient adhered to the prescribed regimen, or that use was maintained during the specified timeframe. Additionally, due to limitations of our data extraction methodology, we were unable to quantify the total duration of GLP-1RA use for exposed individuals. As the majority of adverse events associated with GLP-1RA use occurs within the first month of therapy, we did perform an additional sensitivity analysis to mitigate this limitation, which did not show a difference in incidence of adverse outcomes (20). Third, we were unable to reliably extract A1c values and microvascular/macrovascular complications of diabetes and therefore stratified patients in a binary fashion during the matching process as either having or not having diabetes. Fourth, we did not consider the use of compounded GLP-1RAs, focusing solely on U.S. Food and Drug Administration (FDA)-approved GLP-1RA products. During our medication reconciliation process, compounded medications are specifically identified as such and were not included in our analysis. This exclusion might limit the generalizability of our findings, as we cannot account for the potential differences in treatment outcomes between patients using FDA-approved vs. compounded GLP-1RA formulations. Fifth, many Mayo Clinic Health System ICUs are mixed, housing both surgical and medical patients. We controlled for this by performing a subgroup analysis (surgery within 48 hr of index admission), which did not demonstrate any significant impact on the primary outcomes. Fifth, while the matched cohort methodology ensures balance in observed characteristics between groups, residual confounding due to unobserved or unmeasured variables may still influence the results. Additionally, this methodology may reduce generalizability, as the matched cohort may not fully represent the broader population from which the cohorts were drawn.

In conclusion, pre-ICU GLP-1RA exposure was not associated with increased odds of clinically significant gastrointestinal complications and was instead associated with increased hospital-free days. While the mechanisms behind this association warrant further study, our results highlight the potential role of GLP-1RAs in improving hospital outcomes. Further research should focus on investigating the pathways through which GLP-1RA treatment may enhance recovery and reduce hospitalization duration.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (https://journals.lww.com/ccejournal).

This research was funded through the Mayo Clinic Department of Critical Care Medicine Small Grants Award Program.

The preliminary results of this study have been accepted as an abstract to the American Thoracic Society 2025 International Conference, San Francisco, CA, May 19, 2025.

The authors have disclosed that they do not have any potential conflicts of interest.

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The content is solely the responsibility of the authors and does not necessarily represent the official views of Mayo Clinic.

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