

Pulmonary Aspiration and Related Outcomes Associated with Semaglutide and Tirzepatide: A Comparative Pharmacovigilance Study of the FDA Adverse Event Reporting System (FAERS)

Onat Sarica

onatsarica@gmail.com

Inonu University <https://orcid.org/0009-0009-6944-2847>

Research Article

Keywords: Semaglutide, Tirzepatide, Incretin mimetics, Pulmonary aspiration, Pharmacovigilance, FAERS, Drug safety

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11391047/v1>

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Additional Declarations: The authors declare no competing interests.

Abstract

Background

Incretin-based therapies, including the GLP-1 receptor agonist semaglutide and the dual GIP/GLP-1 receptor co-agonist tirzepatide, delay gastric emptying, raising clinical concerns regarding pulmonary aspiration. This study evaluates serious clinical outcomes among pulmonary aspiration-related adverse event reports and characterizes dual-exposure cases.

Methods

Adverse event reports associated with pulmonary aspiration and aspiration pneumonia were identified from the FDA Adverse Event Reporting System (FAERS). Reports listing both agents as suspect products were segregated into an independent co-reported cohort ($n = 7$). Single-agent semaglutide ($n = 132$) and tirzepatide ($n = 79$) cohorts were analyzed for demographic profiles and serious clinical outcomes (death, hospitalization, and life-threatening events). Fisher's exact tests were performed to compare outcomes between cohorts.

Results

A total of 218 cases were analyzed. In the semaglutide cohort ($n = 132$; mean age 61.1, SD (standard deviation) 14.6 years; 48.5% female), mortality was 17.4% and hospitalization was 62.1%. In the tirzepatide cohort ($n = 79$; mean age 65.2, SD 15.4 years; 51.9% female), mortality was 16.5% and hospitalization was 53.2%. Mortality ($p = 1.000$, OR = 1.071) and hospitalization ($p = 0.2477$, OR = 1.445) showed no significant differences between groups. However, reports designated as life-threatening were significantly more frequent with tirzepatide compared to semaglutide (17.7% vs. 7.6%; $p = 0.0417$, OR = 0.381). In the co-reported cohort ($n = 7$), 57.1% required hospitalization, with no deaths or life-threatening events reported.

Conclusion

Spontaneous reports of pulmonary aspiration associated with semaglutide and tirzepatide demonstrate similar frequencies of mortality and hospitalization, but a higher proportion of life-threatening designations in tirzepatide cases. Identifying and isolating co-reported cases prevents cross-contamination in incretin pharmacovigilance studies.

1. INTRODUCTION

Incretin-based therapeutics have revolutionized the contemporary management of type 2 diabetes mellitus and chronic weight management. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-

1 RA), and tirzepatide, a first-in-class dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor co-agonist, exhibit potent glycemic control and substantial weight reduction efficacy. Mechanistically, in addition to stimulating glucose-dependent insulin secretion and suppressing glucagon release, incretin receptor activation markedly inhibits gastric motility and decelerates gastric emptying.

While delayed gastric emptying contributes beneficially to postprandial satiety and glycemic moderation, it has emerged as a significant source of perioperative and acute clinical vulnerability. Retained gastric content increases the volume and acidity of gastric residual material, significantly elevating the risk of regurgitation and pulmonary aspiration under anesthesia, procedural sedation, or during spontaneous acute illness [1]. Professional anesthesiology societies, including the American Society of Anesthesiologists (ASA), have consequently issued clinical guidance regarding preoperative fasting and perioperative discontinuation intervals for GLP-1 receptor agonists [2].

Despite extensive regulatory trials and post-marketing surveillance, real-world comparative safety evidence evaluating the clinical course and severity of aspiration events associated with single-agent versus dual-exposure incretins remains sparse. Given the heightened potency and dual receptor dynamics of tirzepatide compared to selective GLP-1 agonists, real-world post-marketing safety comparisons are warranted. Furthermore, spontaneous adverse event reporting systems frequently encompass multi-drug exposures that require rigorous segregation to prevent cross-contamination. This study aimed to interrogate the FDA Adverse Event Reporting System (FAERS) to compare demographic characteristics and serious clinical outcomes (mortality, hospitalization, life-threatening designations) among spontaneous pulmonary aspiration reports involving semaglutide and tirzepatide, and to characterize dual-exposure reports as an isolated series.

2. METHODS

2.1 Study Design and Data Source: A retrospective pharmacovigilance cohort study was conducted using post-marketing safety data extracted from the publicly accessible FDA Adverse Event Reporting System (FAERS) Public Dashboard. The surveillance timeframe encompassed reports submitted between January 1, 2023, and October 2, 2026. This investigation adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational cohort studies [3].

2.2 Case Selection and Cohort Definitions: Adverse event records were queried by suspect drug active ingredients: 'Semaglutide' (including Ozempic, Wegovy, Rybelsus) and 'Tirzepatide' (including Mounjaro, Zepbound). Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) specifically denoting pulmonary aspiration were targeted: 'Aspiration', 'Pneumonia Aspiration', and 'Pneumonitis Aspiration'. To ensure analytical purity and mitigate exposure cross-contamination, reports listing both semaglutide and tirzepatide concurrently as suspect products were identified and segregated into an

independent co-reported cohort. The remaining reports constituted the distinct single-agent semaglutide and tirzepatide cohorts.

2.3 Clinical Variables and Outcomes: Extracted demographic variables included age, sex, and reporting indications. Serious adverse event outcomes designated by the FDA were recorded: (1) Death, (2) Hospitalization and (3) Life-threatening events. The non-exclusive nature of FAERS serious outcome coding was preserved, and each endpoint was evaluated independently.

2.4 Statistical Analysis: Continuous variables were summarized using mean, standard deviation (SD), and range. Categorical variables were presented as absolute frequencies and percentages. Comparative outcome frequencies between single-agent semaglutide and tirzepatide cohorts were evaluated using two-tailed Fisher's exact tests conducted via GraphPad QuickCalcs (<https://www.graphpad.com/quickcalcs/contingency1/>). Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated using the MedCalc Odds Ratio Calculator (https://www.medcalc.org/calc/odds_ratio.php). Statistical significance was defined as a two-sided p-value < 0.05.

3. RESULTS

A total of 218 aspiration-related adverse event cases met all inclusion criteria across the reporting window. Initial case queries yielded 139 records for semaglutide and 86 records for tirzepatide. Cross-referencing revealed 7 overlapping case IDs that co-reported both drugs as suspect agents. Following segregation of this dual-exposure cohort (n = 7), the final comparative analytical sample comprised 132 single-agent semaglutide cases and 79 single-agent tirzepatide cases.

3.1 Demographic Profiles: In the semaglutide cohort (n = 132), the mean age was 61.1 years (SD 14.6; range 21–91 years). Females constituted 48.5% (n = 64), males accounted for 37.9% (n = 50), and sex was unspecified in 13.6% (n = 18). In the tirzepatide cohort (n = 79), the mean age was 65.2 years (SD 15.4; range 30–93 years). Females constituted 51.9% (n = 41), males accounted for 35.4% (n = 28), and sex was unspecified in 12.7% (n = 10). Age and sex distributions were comparable between cohorts.

3.2 Serious Clinical Outcomes: Comparative clinical outcomes between the single-agent cohorts are summarized in Table 1.

Outcome	Semaglutide (n=132)	Tirzepatide (n=79)	Odds Ratio (OR)*	95% CI*	p-value †
Death	23 (17.4%)	13 (16.5%)	1.071	0.508 – 2.258	1.000
Hospitalization	82 (62.1%)	42 (53.2%)	1.445	0.821 – 2.541	0.2477
Life-Threatening	10 (7.6%)	14 (17.7%)	0.381	0.160 – 0.904	0.0417

* Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated using the MedCalc Odds Ratio Calculator (reference: tirzepatide). An OR < 1 denotes lower odds in the semaglutide cohort.

† p-values were calculated using two-tailed Fisher's exact tests conducted via GraphPad QuickCalcs. Statistical significance is defined as $p < 0.05$.

Mortality demonstrated no statistically significant difference between semaglutide and tirzepatide (17.4% vs. 16.5%; OR = 1.071, 95% CI 0.509-2.258, $p = 1.000$). Similarly, hospitalization rates did not differ significantly between groups (62.1% vs. 53.2%; OR = 1.445, 95% CI 0.821-2.541, $p = 0.2477$). In contrast, reports classified as life-threatening events were significantly higher in the tirzepatide cohort compared to the semaglutide cohort (17.7% vs. 7.6%; OR = 0.381, 95% CI 0.160-0.904, $p = 0.0417$).

3.3 Characterization of the Co-Reported Cohort ($n = 7$): The segregated dual-exposure series (mean age 59.2, SD 2.9 years; 42.9% female, 28.6% male) involved cases where both semaglutide and tirzepatide were cited. In this group, 57.1% required hospitalization. Crucially, zero deaths and zero life-threatening designations were documented in this subset.

4. DISCUSSION

In this comprehensive pharmacovigilance evaluation of the FDA FAERS database, pulmonary aspiration adverse events linked to semaglutide and tirzepatide exhibited high overall severity, with hospitalization exceeding 50% and mortality exceeding 16% across both cohorts. While mortality and hospitalization frequencies were statistically indistinguishable between the two incretin agents, tirzepatide demonstrated a significantly higher proportion of life-threatening event designations compared to semaglutide (17.7% vs. 7.6%, $p = 0.0417$).

The heightened frequency of life-threatening designations for tirzepatide warrants careful pharmacological and epidemiological contextualization. Biologically, tirzepatide is a unimolecular dual GIP and GLP-1 receptor agonist. The synergistic activation of both receptor pathways confers profound slowing of gastrointestinal transit and gastric tone [4]. Enhanced decrements in proximal gastric relaxation could plausibly translate into larger residual intragastric volumes, potentially predisposing to higher-acuity aspiration events requiring urgent airway management or intensive resuscitation.

From an epidemiological perspective, post-marketing reporting artifacts must be taken into consideration. Tirzepatide received regulatory approvals (Mounjaro in 2022, Zepbound in late 2023) substantially more recently than semaglutide. In spontaneous reporting systems, newly approved pharmacological entities such as tirzepatide often experience reporting bias driven by heightened clinical scrutiny and selective reporting of severe or life-threatening outcomes compared to mature agents (a phenomenon often associated with notoriety bias and evolving post-marketing surveillance) [5]. Confounding by indication and rapid dose-escalation dynamics may also contribute.

A key methodological contribution of this study is the formal identification and segregation of co-reported cases ($n = 7$). In spontaneous reporting databases, switching between incretin agents during wash-out periods or dual prescribing can lead to simultaneous reporting. Failure to separate these cases creates mutual contamination between comparative arms. Segregating them ensures analytical independence while providing descriptive insight into transitional incretin exposure.

Study Limitations: Spontaneous reporting systems such as FAERS possess inherent limitations, including variable report completeness, passive voluntary submission bias, lack of total denominator exposure data, and inability to definitively establish biological causality. Specific clinical variables such as exact fasting duration prior to procedural aspiration, BMI, anesthetic regimens, and concurrent prokinetic or opioid use could not be universally extracted. Consequently, these findings should be interpreted as robust safety signals highlighting procedural and acute management vigilance rather than causal incidence rates.

5. CONCLUSION

Spontaneous FAERS reports of pulmonary aspiration associated with semaglutide and tirzepatide demonstrate comparable and concerning rates of mortality and hospitalization, but tirzepatide is characterized by a significantly higher proportion of life-threatening designations. Clinicians and anesthesiologists should maintain strict perioperative fasting adherence and acute airway vigilance across all incretin regimens. Methodological isolation of co-reported multi-drug cases should become a standard practice in incretin pharmacovigilance.

Declarations

Ethics Approval: Ethical review and institutional oversight approval were not required as this study analyzed solely publicly accessible, de-identified post-marketing surveillance data from the FDA FAERS database.

Competing Interests: The author declares that they have no competing financial or non-financial interests.

Funding: This research received no external funding or financial sponsorship.

Data Availability: All data supporting the findings of this study are available within the manuscript and supplementary files. Raw adverse event records are publicly accessible via the FDA FAERS Public Dashboard.

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Supplementary Files

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