Real World Obesity and GLP 1RA Tolerability: Incidence and Indicators of Serious GI Adverse Events Using Federated Learning

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Introduction

- **GLP-1 receptor agonists (RAs) have significantly advanced obesity management by providing notable weight reduction.** While serious gastrointestinal (GI) complications are established in controlled GLP-1 RA trials (1), real-world incidence and risk stratification remain poorly defined. Traditional centralized prediction models are often constrained by data-sharing limitations and heterogeneity across institutions, impeding their robustness and generalizability. To overcome these challenges, federated learning (FL) enables privacy-preserving analytics by training models on decentralized data by sharing only aggregated statistics. This approach addresses regulatory barriers, but its benefits have not been fully leveraged in obesity studies
- This study aims to **estimate the incidence of serious GI adverse events and identify risk estimates in patients treated with GLP-1 RAs, leveraging FL** to address real-world evidence gaps and ensure privacy in distributed analytics

Methods

- **A retrospective cohort study using federated learning across five primary care healthcare databases** in USA, Belgium, France, Germany, Spain, **standardized using OMOP Common Data Model**
- Eligible **adults living with obesity (BMI ≥30) initiated GLP-1 RA** between approval dates (June 2021-March 2022) and latest data (late 2025). Individuals with diabetes (T1D & T2D) were excluded. The study used an on-treatment design to track the incidence of serious GI diseases within 365 days after initiation
- **Federated Cox models estimated GI events and hazard ratios** for covariates such as age, sex, baseline BMI, prior GI history, and comorbidities. All analyses were conducted locally using a federated learning infrastructure (Vantage6)

Results

- **The federated analysis included 356,162 adults with obesity** across five databases (mean age 51.7 ± 13.8 years; 71.3% female; mean BMI 37.3 ± 4.6 kg/m²). Semaglutide accounted for 71.0% and tirzepatide for 29.8% of initiations, with approximately 2,900 patients (~0.8%) appearing in both treatment strata
- **Within 365 days of GLP-1RA initiation, 60,356 of 356,154 patients (16.9%) experienced a composite GI adverse event.** The median time to first event was 82 days, with over half of events occurring within the first three months – A period that may correspond to dose titration. Unadjusted event proportions were 18.1% for semaglutide and 14.2% for tirzepatide. These descriptive differences are not adjusted for differential follow-up (mean 525 vs. 328 days) or baseline GI risk and should not be interpreted as comparative safety estimates
- **The most frequently observed component events were gastritis (1.95%), esophagitis (1.30%), GI hemorrhage (1.05%), and cholelithiasis (0.97%).** Pancreatitis (0.17%), gastroparesis (0.20%), and intestinal obstruction (0.15%) were less common but observed at measurable frequencies in this cohort
- The federated Cox model retained six of ten prespecified covariates after automated diagnostics. Treatment variables (semaglutide, tirzepatide) were excluded due to collinearity; accordingly, this model estimates prognostic risk factors rather than comparative drug effects
- **Prior serious GI event history within two years before initiation was the dominant predictor (HR 1.304, 95% CI 1.280–1.330, p < 0.001),** corresponding to approximately 30% higher risk of a subsequent GI event. **BMI showed a small inverse association (HR 0.995 per kg/m², p < 0.001).** Female sex (HR 1.025, p = 0.010) and dyslipidemia (HR 1.018, p = 0.038) were statistically significant but of modest magnitude. All six coefficients were contributed by all five participating sites, confirming model convergence across healthcare systems
- When baseline risk factors were compared through their combined effect on the hazard, **prior GI history alone accounted for a +30.4% increase in relative hazard** compared to the reference profile. By contrast, **the combined effect of female sex, dyslipidemia, and hypertension was +2.9%**

Conclusion

- **In this federated analysis of 356,162 adults with obesity across five international databases, prior GI event history emerged as the dominant predictor of GI adverse events following GLP-1RA initiation – Contributing approximately 10 times more to patient-level risk than demographic and cardiometabolic factors combined.**
- **With a median time to first event of 82 days, events were concentrated in the early post-initiation period, which may correspond to dose titration.**
- **Compared with traditional federated approaches, this FL framework enables more scalable, privacy-preserving model training across large, globally distributed obesity datasets – Without transferring raw patient-level information or requiring centralised data pooling – Thereby improving the accuracy and generalisability of GI risk prediction in GLP-1 RA therapy and better supporting personalised, safer clinical decision-making.**

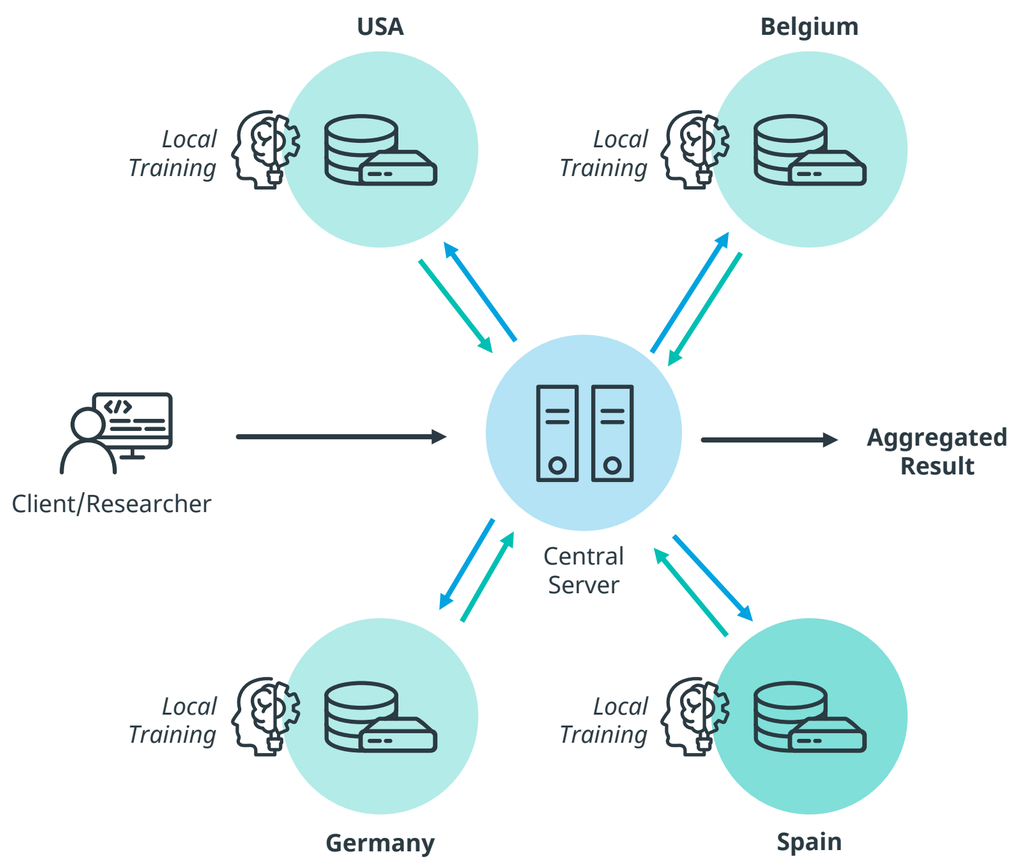

Figure 1. Schematic overview of the federated learning model

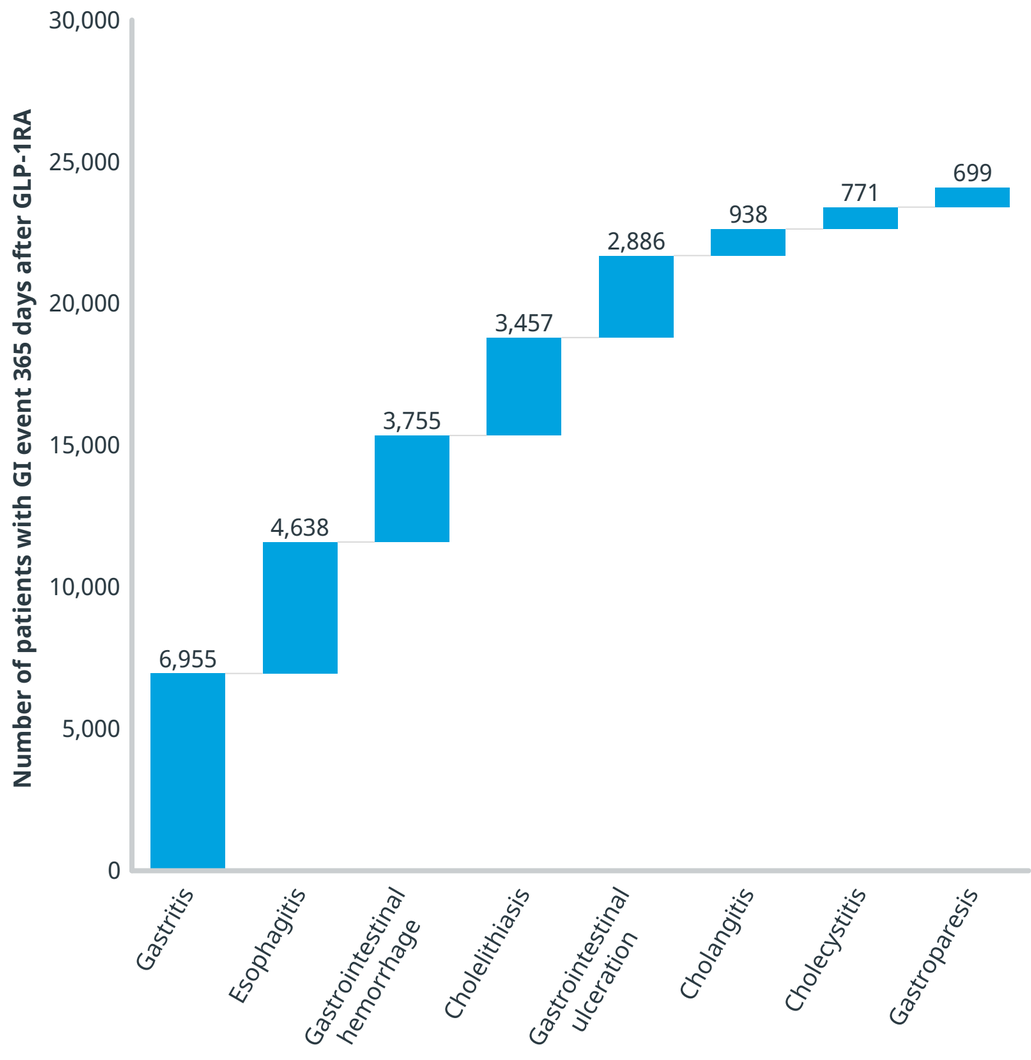

Figure 2. Gastrointestinal event spectrum waterfall

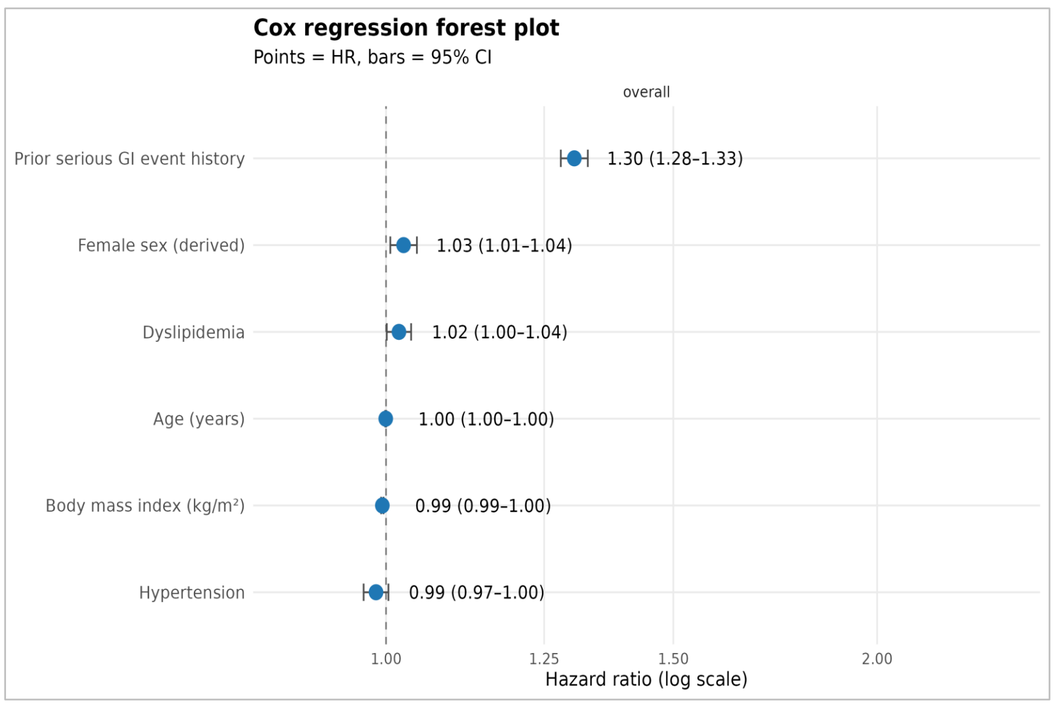

Figure 3. Forest plot outlining hazard ratios for specific covariates

[1]Chiang CH, Jaroenlapnopparat A, Colak SC, Yu CC, Xanthavanij N, Wang TH, See XY, Lo SW, Ko A, Chang YC, Song J, Hsia YP, Chiang CH. Glucagon-Like Peptide-1 Receptor Agonists and Gastrointestinal Adverse Events: A Systematic Review and Meta-Analysis. Gastroenterology. 2025 Nov;169(6):1268-1281

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