Supplemental Online Content

Dixit AA, Bateman BT, Hawn MT, et al. Preoperative GLP-1 receptor agonist use and risk of postoperative respiratory complications. *JAMA*. doi:10.1001/jama.2024.5003

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Diagnostic and Procedural Codes Used to Define Emergency Surgeries Included in Study[a]

Type of Surgery	ICD-10 codes	CPTs
Laparoscopic appendectomy[1,2]	K35.X K36.X K37.X	44950 44970 44960
Laparoscopic cholecystectomy[3]	K80.1X K80.0X K81.X	47562 47563 47564 47600 47605 47610 47612 47620 47630
Operative management of traumatic hip fracture[4]	S72001B, S72001C, S72002A, S72002B, S72002C, S72009A, S72009B, S72009C, S72011A, S72011B, S72011C, S72012A, S72012B, S72012C, S72019A, S72002B, S72002C, S72009A, S72009B, S72009C, S72011A, S72011B, S72011C, S72012A, S72012B, S72012C, S72019A, S72019B, S72019C, S72031A, S72031B, S72031C, S72032A, S72032B, S72032C, S72033A, S72033B, S72033C, S72034A, S72034B, S72034C, S72035A, S72035B, S72035C, S72036A, S72036B, S72036C, S72041A, S72041B, S72041C, S72042A, S72042B, S72042C, S72043A, S72043B, S72043C, S72044A, S72044B, S72044C, S72045A, S72045B, S72045C, S72046A, S72046B, S72046C, S72051A, S72051B, S72051C, S72052A, S72052B, S72052C, S72059A, S72059B, S72059C, S72061A, S72061B, S72061C, S72062A, S72062B, S72062C, S72063A, S72063B, S72063C, S72064A, S72064B, S72064C, S72065A, S72065B, S7206SC, S72066A, S72066B, S72066C, S72091A, S72091B, S72091C, S72092A, S72092B, S72092C, S72099A, S72099B, S72099C, S72101A, S72101B, S72101C, S72102A, S72102B, S72102C, S72109A, S72109B, S72109C, S72111A, S72111B, S72111C, S72112A,	27125 27130 27230 27232 27235 27236 27246 27248 73530

	S72112B, S72112C, S72113A, S72113B, S72113C, S72114A, S72114B, S72114C, S72115A, S72115B, S72115C, S72116A, S72116B, S72116C, S72121A, S72121B, S72121C, S72122A, S72122B, S72122C, S72123A, S72123B, S72123C, S72124A, S72124B, S72124C, S72125A, S72125B, S72125C, S72126A, S72126B, S72126C, S72131A, S72131B, S72131C, S72132A, S72132B, S72132C, S72133A, S72133B, S72133C, S72134A, S72134B, S72134C, S72135A, S72135B, S72135C, S72136A, S72136B, S72136C, S72141A, S72141B, S72141C, S72142A, S72142B, S72142C, S72143A, S72143B, S72143C, S72144A, S72144B, S72144C, S72145A, S72145B, S72145C, S72146A, S72146B, S72146C, S7221XA, S7221XB, S7221XC, S7222XA, S7222XB, S7222XC, S7223XA, S7223XB, S7223XC, S7224XA, S7224XB, S7224XC, S7225XA, S7225XB, S7225XC, S7226XA, S7226XB, S7226XC	

Colectomy for diverticulitis[5]	K57.32 K57.33	44110 44111 44130 44139 44140 44141 44143 44144 44145 44156 44147 44150 44151 44155 44156 44157 44158 44160 44320 44187 44188 44204 44205 44206 44207 44208 44210 44211 44212 44213 44227 44238
Operative management of adhesive small bowel obstruction[6]	K56.50 K56.51 K56.52	44180 44005
Operative management of ovarian torsion	N83.5	58661 58662 58670
Operative management of testicular torsion	N44.0	54640 54650 54692
Operative management of ectopic pregnancy[7]	O00 O000 O001 O002 O008 O009	59120 59121 59130 59135 59136 59140 59150 59151 58770 58673 58700 58720 49320 58661 58679

Operative management of incarcerated or strangulated hernia[8]	K40.X K41.X K42.X K43.X K44.X K45.X K46.X	49521 49553 49557 49561 49566 49572 49587 49650 49653 49655 49657
Laparoscopic or open repair of perforated peptic or duodenal ulcer[9]	K25.1X K25.2X K25.5X K25.6X K26.1X K26.2X K26.5X K26.6X	43631 43632 43633 43625 43659 44238 49329 43840 44602 44603 49000 49905
Transurethral intervention for nephrolithiasis	N20.X N21.X N22.X	52005 52310 52332 52352 52353 52356 50590 52317 52318
Upper endoscopy for foreign body removal	T18.1X T18.2X T18.3X	43215 43247
Upper endoscopy for management of bleeding peptic or duodenal ulcer[10]	K25.2X K25.6X K26.2X K26.6X K27.2X K27.6X K28.2X K28.6X K25.0X K25.4X K26.0X K26.4X K27.4X K28.0X K28.4X	43227 43255 44366 44378

[a]Patients were included in the study if they had an emergency department code with a listed ICD-10 diagnostic code on the same day as a corresponding CPT surgical procedural code. The X symbol following a decimal in the ICD-10 codes represents a wildcard (i.e., either no subsequent character, or any alphanumeric character).

eMethods 1. Sample Creation, Definitions of Variables, and Statistical Approach

Patients were included in our study if they were age ≥18 years and continuously enrolled in a Merative MarketScan®[11] plan for 210 days before and 8 days after their date of surgery. Date of surgery was restricted to 1/1/2015 through 12/31/2021. The sample was further restricted to those with type 2 diabetes, defined as having at least one ICD-10 diagnosis code for type 2 diabetes plus a prescription fill for at least one oral antidiabetic medication or evidence of insulin use[12] in the 210 days preceding surgery. Oral antidiabetic medications included alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase IV inhibitors, meglitinides, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), amylinomimetics (i.e., pramlintide), sodium glucose transport protein 2 inhibitors, sulfonylureas, and thiazolidinediones. Use of insulin was defined as any prescription fills for insulin or glucagon. Medications were defined using National Drug Code (NDCs) as assigned using the MarketScan Redbook.[13]

We defined the exposure as those with prescription fills for a GLP-1 RA with days-supply overlapping with the date-of-surgery.

We defined the outcome as a composite binary outcome using ICD-10 codes encompassing aspiration pneumonitis and postoperative respiratory failure[14] (as presented in eTable 2), or as admission to the intensive care unit (ICU) based on revenue codes 0200-0205, 0207-0213, or 0219,[15] in the 0-7 days following date-of-surgery. We included ICU-level care given that: 1) most patients undergoing the 13 selected surgeries would not be expected to require ICU-level postoperative care, and 2) unexpected post-operative respiratory failure is one of the most common reasons for unanticipated ICU admission.[16] The exposure was defined using diagnoses found in the MarketScan Inpatient Services and Outpatient Claims files. Both files contain claims with the actual dates-of-service (rather than discharge date) for professional encounters and services.

Covariates included age, sex, Diabetes Complications Severity Index,[17] number of pharmacologic classes used to treat diabetes, use of insulin, Elixhauser comorbidities,[18] year fixed effects, and surgical procedure fixed effects. The Diabetes Complications Severity Index is a severity score ranging from 0 to 13 and validated for use with ICD-10 diagnosis codes in administrative data. It is based on the sum of individual scores of 0 to 2 for diabetes-related complications in seven categories (cardiovascular, cerebrovascular and peripheral vascular disease, metabolic disease, nephropathy, retinopathy, and neuropathy). Diabetes Complications Severity Index was calculated with points assigned if the patient had at least one relevant ICD-10 diagnosis code by category in the previous 210 days. Elixhauser comorbidities were also assigned if the patient had at least 1 claim with a relevant ICD-10 diagnosis code in the previous 210 days. We excluded two Elixhauser comorbidities (diabetes with and without complications) to avoid collinearity with the Diabetes Complications Severity Index. Number of pharmacologic classes was assigned based on the number of unique pharmacologic classes (oral antidiabetic medications, as defined above, plus insulin) with days-supply overlapping with the date-of-surgery.

We first calculated absolute standardized mean differences (SMDs) between patients exposed versus unexposed to GLP-1 RAs across all covariates and fixed effects mentioned above. SMD greater than 0.1 was considered a meaningful difference in prevalence between groups.

We then estimated a multivariable logistic regression model with the dependent variable set as the composite binary outcome variable, and the primary independent variable set at use of GLP-1 RA medication. We adjusted for all covariates listed above. The odds ratio was then converted to predicted means (as presented in Table 2) by calculating the average predicted probability of the outcome if all patients in the study population had received a GLP-1 RA or had not received a GLP-1 RA, keeping all other covariates and fixed effects as is.

eTable 2. Diagnostic Codes Used to Define Postoperative Respiratory Complications

	ICD-10
Postoperative Respiratory Failure	J95.821
	J95.822
	J96.00
	J96.01
	J96.02
	J96.10
	J96.11
	J96.12
	J96.20
	J96.21
	J96.22
	J96.90
	J96.91
	J96.92
	Z99.11
	Z99.12
Aspiration pneumonitis	J69.0
	J69.8

eMethods 2. Description of Sensitivity Analyses

We conducted three additional analyses as checks for robustness.

First, we replicated the primary analysis but respecified the outcome as a composite binary variable encompassing only the diagnosis codes in eTable 2 (i.e., we omitted admission to the ICU from the definition).

Second, we re-estimated the model using targeted maximum likelihood estimation (TMLE)[19] using the same analytic sample used in the primary analysis. We chose this approach as a sensitivity analysis given that it is a doubly robust method; thus, it can better approximate causal effects and circumvent potential biases in estimates derived from standard multivariable logistic regression models. Further, given the large number of covariates in our administrative dataset, we applied TMLE via the SuperLearner, a machine learning ensembling method with 10-fold cross validation. We included the following algorithms in the SuperLearner using the SuperLearner package in R:[20,21] SL.mean, SL.glm, SL.glm.interaction, and SL.glmnet. These algorithms encompassed standard logistic regression with and without interaction terms and elastic net regression. The 95% confidence interval for the average treatment effect was calculated from 500 bootstrap resamples with replacement. This model was estimated using R Statistical Software V.4.2.3.

Third, we replicated the primary analysis but restricted the analytic sample to those undergoing surgeries considered lower risk for aspiration and for post-operative complications (laparoscopic appendectomy, laparoscopic cholecystectomy, and transurethral intervention for urolithiasis/nephrolithiasis; N=18,585).

eReferences

1. Harbaugh CM, Lee JS, Hu HM, McCabe SE, Voepel-Lewis T, Englesbe MJ, Brummett CM, Waljee JF: Persistent Opioid Use Among Pediatric Patients After Surgery. Pediatrics 2018; 141
2. Loehrer AP, Leech MM, Weiss JE, Markey C, Wengle E, Aarons J, Zuckerman S: Association of Cost Sharing With Delayed and Complicated Presentation of Acute Appendicitis or Diverticulitis. JAMA Health Forum 2021; 2: e212324
3. Lois A, Fennern E, Cook S, Flum D, Davidson G: Patterns of care after cholecystostomy tube placement. Surg Endosc 2022; 36: 2778-2785
4. Montgomery JR, Neiman PU, Brown CS, Cain-Nielsen AH, Scott JW, Sangji NF, Oliphant BW, Hemmila MR: Sources of Postacute Care Episode Payment Variation After Traumatic Hip Fracture Repair Among Medicare Beneficiaries: Cross-Sectional Retrospective Study. Ann Surg Open 2022; 3: e218
5. Simianu VV, Fichera A, Bastawrous AL, Davidson GH, Florence MG, Thirlby RC, Flum DR: Number of Diverticulitis Episodes Before Resection and Factors Associated With Earlier Interventions. JAMA Surg 2016; 151: 604-10
6. Carmichael SP, 2nd, Kline DM, Mowery NT, Miller PR, 3rd, Meredith JW, Hanchate AD: Geographic Variation in Operative Management of Adhesive Small Bowel Obstruction. J Surg Res 2023; 286: 57-64
7. Wall-Wieler E, Shover CL, Hah JM, Carmichael SL, Butwick AJ: Opioid Prescription and Persistent Opioid Use After Ectopic Pregnancy. Obstet Gynecol 2020; 136: 548-555
8. Senkowski C, Savarise M, Roth JS, Nagle J: Hernia repair and complex abdominal wall reconstruction. Access Date Nov 15 2023. https://www.facs.org/for-medical-professionals/news-publications/news-and-articles/bulletin/2017/04/hernia-repair-complex-abdominal-wall-reconstruction/.
9. Jayaraman SS, Allen R, Feather C, Turcotte J, Klune JR: Outcomes of Laparoscopic vs Open Repair of Perforated Peptic Ulcers: An ACS-NSQIP Study. J Surg Res 2021; 265: 13-20
10. Quan S, Frolkis A, Milne K, Molodecky N, Yang H, Dixon E, Ball CG, Myers RP, Ghosh S, Hilsden R, van Zanten SV, Kaplan GG: Upper-gastrointestinal bleeding secondary to peptic ulcer disease: incidence and outcomes. World J Gastroenterol 2014; 20: 17568-77
11. Stanford Center for Population Health Sciences: MarketScan Databases (version 3.0) [data set]. Redivis (RRID:SCR_023111). Access Date Nov 25 2023. https://doi.org/10.57761/kg3j-nh50.
12. Schapiro D, Juneja R, Huang A, Meeks A, Liu D, Gelsey FT, Perez-Nieves M: Real-World Patterns of Basal Insulin Use with Other Diabetes Medications Among People with Type 2 Diabetes Between 2014 and 2020. Diabetes Ther 2023; 14: 1157-1174
13. Stanford Center for Population Health Sciences: MarketScan Redbook (version 2.1) [data set]. Redivis (RRID:SCR_023111). Access Date Nov 25 2023. https://doi.org/10.57761/pxk9-dx75.
14. Agency for Healthcare Quality and Research: Patient Safety Indicator 11 (PSI 11) Postoperative Respiratory Failure Rate. Access Date October 15 2023. https://qualityindicators.ahrq.gov/Downloads/Modules/PSI/V2022/TechSpecs/PSI_11_Postoperative_Respiratory_Failure_Rate.pdf.
15. Kannan S, Song Z: Changes in Out-of-Pocket Costs for US Hospital Admissions Between December and January Every Year. JAMA Health Forum 2023; 4: e230784

16. Haller G, Myles PS, Wolfe R, Weeks AM, Stoelwinder J, McNeil J: Validity of unplanned admission to an intensive care unit as a measure of patient safety in surgical patients. Anesthesiology 2005; 103: 1121-9
17. Wicke FS, Glushan A, Schubert I, Koster I, Lubeck R, Hammer M, Beyer M, Karimova K: Performance of the adapted Diabetes Complications Severity Index translated to ICD-10. Am J Manag Care 2019; 25: e45-e49
18. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43: 1130-9
19. Schuler MS, Rose S: Targeted Maximum Likelihood Estimation for Causal Inference in Observational Studies. Am J Epidemiol 2017; 185: 65-73
20. Polley E, van der Laan M: SuperLearner: Super Learner Prediction, Package Version 2.0-28.1. Access Date Nov 30 2023. https://cran.r-project.org/package=SuperLearner.
21. R Core Team: R: A language and environment for statistical computing. Access Date Nov 30 2023. https://www.R-project.org/.