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Incidence and Risk Factors for New Onset Diabetes Mellitus Following Surgical Resection of Pancreatic Cystic Lesions: A MarketScan Study

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Abstract

Objectives: There is a paucity of literature evaluating new-onset diabetes mellitus (NODM) following resection of pancreatic cystic lesions (PCLs). We sought to characterize the incidence and risk factors associated with NODM following partial pancreatectomy for PCLs.

Methods: We utilized the IBM MarketScan Database (2012–2018) to identify all non-diabetic adults who underwent partial pancreatectomy for PCLs. Patients with any other pancreatic disease were excluded. We performed Kaplan-Meier analysis and multivariable Cox proportional hazards regression to define the incidence and risk factors of postoperative NODM.

Results: Among 311 patients, the overall risk (95% confidence interval) of NODM was 9.1% (6.3–12.9%), 15.1% (11.3–20.2%), and 20.2% (15.3–26.4%) at six, 12 and 24 months,

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respectively. Multivariable analysis (adjusted hazard ratio, 95% confidence interval) revealed that older age (1.97, 1.04–3.72; 55–64 vs 18–54 years), obesity (2.63, 1.35–5.12), hypertension (1.79, 1.01–3.17), and cardiovascular disease (2.54, 1.02–6.28) were independent predictors of NODM. Rates of NODM were similar following distal pancreatectomy versus pancreaticoduodenectomy.

Conclusions: Within two years, one in five patients without any other pancreatic disease will develop NODM following partial pancreatectomy for PCLs. Those with advanced age, metabolic syndrome features, and/or cardiovascular disease may benefit from preoperative counselling and intensive postoperative monitoring, education, and treatment for DM.

Keywords

pancreatic cystic lesion; pancreatectomy; diabetes mellitus; population database; intraductal papillary mucinous neoplasm

Introduction

Pancreatogenic diabetes, also described as type 3c diabetes mellitus (DM), refers to DM secondary to a disease of the exocrine pancreas, including acute and chronic pancreatitis, pancreatic cancer, cystic fibrosis, and pancreatectomy.[1,2] Regarding pancreatic surgery, pancreaticoduodenectomy (PD) and distal pancreatectomy (DP) can result in DM for a subset of patients, primarily due to loss of islet cell mass; a total pancreatectomy causes obligatory DM. Nearly 3800 elective pancreatectomies are performed each year in the US for a variety of indications.[3,4] The incidence and associated risk factors for new onset diabetes mellitus (NODM) following pancreatectomy varies widely, and may be related, in part, to differences in the underlying pancreatic disorder.[5–7]

Previous single and multi-center studies have noted that the risk of NODM following PD or DP in patients with normal preoperative endocrine function ranges from 18–40%.[8–18] Differences in the type and extent of resection, as well as variations in preoperative patient characteristics, may contribute to the observed variability in NODM. In the most recent and largest systematic review, the pooled estimates for NODM were 21% following DP, 16% following PD, and 6% following central pancreatectomy.[19] The increased density of insulin-producing β-islet cells in the pancreatic body and tail is believed to contribute to the higher risk of NODM following distal pancreatic resections, however, this is an ongoing area of investigation.[20–22]

Pancreatic cystic lesions (PCLs) are increasingly diagnosed due to advancements in cross-sectional imaging techniques, detected in 2.5% of all adults using computed tomography and 13.5–19.5% using magnetic resonance imaging.[23–25] The current standard of care for PCLs with advanced features (symptomatic, presence of a mural nodule or solid component, main pancreatic duct dilation >5 mm or change in duct diameter with upstream atrophy, size ≥3 cm, rapid increase in size, or high grade dysplasia) is surgical resection for patients with satisfactory operative fitness.[26] Patient selection is of particular importance considering the relatively high morbidity (30–40%) of pancreatic surgery and potential perioperative mortality (1–2%).[27] The broad biologic behavior, lack of diagnostic tools, difficulty in the accurate diagnosis of cyst type and risk of malignancy, and the risk of

complications following pancreatectomy necessitates a multidisciplinary team approach for appropriate management decisions. Despite the growing need for individualized care planning, preoperative counselling and intensified post-operative monitoring, to our knowledge, there are no studies evaluating the incidence or risk factors for NODM following elective pancreatectomy specifically for PCLs. Hence, we conducted a retrospective cohort study using a nationally representative population database to evaluate the incidence and identify risk factors for post-operative NODM among patients undergoing partial pancreatectomy for PCLs.

MATERIALS AND METHODS

Study Design and Data Source

This analysis is a retrospective, longitudinal study of the IBM MarketScan Research Database® from 2012 to 2018. This database is a publicly available population-based dataset. As such, the study was exempt from approval by the Ohio State University Institutional Review Board.

The MarketScan Database is compiled and maintained by Truven Health Analytics® and IBM Watson Health (Armonk, NY). MarketScan is one of the largest collections of claims data from insured employees and their dependents, early retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continuers and Medicare-eligible retirees with employer-provided Medicare Supplemental plans in the US. These databases capture individual-level claims data on healthcare utilization, expenditures, diagnoses and pharmaceutical claims at both inpatient and outpatient levels to longitudinally track over 250 million unique, de-identified patients from all 50 states across the continuum of healthcare.[28, 29]

The database was queried using *International Classification of Diseases*, Ninth Edition Clinical Modification (ICD-9-CM) diagnostic codes from January, 2012 to September, 2015 and *International Classification of Diseases*, Tenth Edition Clinical Modification (ICD-10-CM) diagnostic codes from October, 2015 to December, 2018 to define variables of interest (Supplemental Table 1). The transition from ICD-9-CM to ICD-10-CM clinical practice coding in 2015 was replicated in this study with appropriate code conversion. Current Procedural Terminology (CPT) as well as ICD-9/10 Procedural Coding System codes were used to comprehensively capture all medical procedures. Adult patients (age ≥18) with an inpatient or outpatient diagnosis of a PCL who underwent partial pancreatectomy were eligible for inclusion. Rigorous stepwise multi-level exclusion criteria (Fig. 1) were then applied to identify a selective cohort of patients without existing DM prior to surgery. Patients with pregnancy, total pancreatectomy, necrosectomy following acute pancreatitis (AP), islet cell transplantation, prior pancreatic surgery, AP within 6 months prior to surgery, and other causes of pancreatogenic DM (chronic pancreatitis, cystic fibrosis, hemochromatosis, pancreatic cancer) were also excluded. Patients without prior data or sufficient follow up (<1 month after surgery) were further excluded (Supplemental Table 2).

The MarketScan Commercial Claims and Encounters Database includes claims data on patients 18–64 years of age with private or employer-based health insurance. Data from

Medicare claims are not included in the Commercial Claims and Encounters database. The Medicare Supplemental Database contains data from patients age 65 years and older who have supplemental insurance. The Medicare Supplemental Database contains both Medicare claims and supplemental insurance claims for included patients. Of the 311 patients included in final analysis, 77 (24.7%) were derived from the Medicare supplemental database.

Demographic and Clinical Data

Baseline characteristics included age, sex, demographic region, and comorbidities. Other variables included type of resection (distal, proximal, enucleation), open versus laparoscopic surgery, duration of follow-up available, and Charlson Comorbidity Index.[30] Specific ICD and CPT coding for all procedures and variables of interest are noted in Supplemental Table 1. For the purpose of this study, proximal pancreatectomy with duodenectomy (ie, Whipple procedure) was not differentiated from proximal pancreatectomy without duodenectomy.

Statistical Analysis

Demographics were summarized as mean and standard deviation or median and interquartile range for continuous variables and count and percentage for categorical variables. The primary statistical outcome was time from surgery to development of NODM (Fig. 2). Patients who did not develop NODM during the available follow-up period were censored at the latest available follow-up date. For the purposes of this study, NODM was defined as two or more outpatient visits or one inpatient admission with a diagnosis of DM, or starting a new diabetic medication (Supplemental Table 3).[31] A Kaplan-Meier curve was generated to visualize time to NODM and the Kaplan-Meier estimator was used to estimate incidence of NODM at the selected time points, overall and by patient characteristics.

The secondary outcomes were risk factors associated with NODM. Univariable Cox proportional hazards models were fit to evaluate associations between patient characteristics and time to NODM. A multivariable Cox proportional hazards model was fit to identify independent risk factors for NODM. Variables with $P < 0.1$ in univariable modeling (age, sex, region, surgery type, hypertension, hyperlipidemia, obesity, and cardiovascular disease/heart failure) were considered as candidates for the final multivariable model. Backward selection with inclusion criteria $P < 0.05$ was used to select the final multivariable model. Variables with $P < 0.01$ in univariable modeling were kept in the multivariable model regardless of P value. All two-way interactions were tested. Proportional hazards assumptions were evaluated by Kaplan-Meier plots and Schoenfeld residual plots. All two-way interactions were tested using the $P < 0.05$ criteria. Statistical analyses were performed using SAS version 9.4 (Cary, NC).

RESULTS

Baseline Characteristics

A total of 2006 partial pancreatectomies were performed for PCLs from 2012–2018. After the application of stepwise multi-level exclusion criteria, 311 unique patients with otherwise normal pancreatic parenchyma and without pre-existing DM were identified (Fig. 1, Supplemental Table 2). Patient characteristics are demonstrated in Table 1. The median

follow-up time was 16.8 months (interquartile range, 7.2–32.4 months). The mean age of the study cohort was 56.2 (standard deviation, 14.1) years. The majority of patients was female (76.2%). While 218 (70.1%) patients underwent DP, 68 (21.9%) underwent PD, and the excision type was unknown in the remaining 25 (8%).

Time-to-Event Analysis

Kaplan-Meier analysis was utilized to assess time to development of NODM following partial pancreatectomy for a PCL. The curve is shown in Figure 3 and corresponding incidence rates at select time points are listed in Table 2. The estimated incidence of NODM was 9.1% (95% confidence interval [CI], 4.5–10.3%) at 6 months, 15.1% (95% CI, 11.3–20.1%) at 12 months, and 20.2% (95% CI, 15.3–26.4%) at 24 months.

Predictors of NODM Following Surgery

Univariable Cox proportional hazard models (Table 3) for time to DM were utilized to identify characteristics associated with NODM and produce corresponding hazard ratios (HR). Patients age 55–64 years (HR, 2.42, 95% CI, 1.33–4.41), male sex (HR, 2.23, 95% CI, 1.29–3.84), hypertension (HR, 2.23, 95% CI, 1.31–3.79), obesity (HR, 2.32, 95% CI, 1.22–4.42), hyperlipidemia (HR, 1.90, 95% CI, 0.99–3.63), and presence of ≥3 Charlson Comorbidity Index (HR, 1.78, 95% CI, 1.01–3.15) were associated with increased risk of NODM. Multivariable results are shown in Table 4. Patients in the age group of 55–64 years (adjusted hazard ratio [aHR], 1.97, 95% CI, 1.04–3.72), obesity (aHR, 2.63, 95% CI, 1.35–5.12), hypertension (aHR, 1.79, 95% CI, 1.01–3.17) and cardiovascular disease/heart failure (aHR, 2.54, 95% CI, 1.02–6.28) were identified as independent risk factors of NODM following pancreatectomy for PCLs.

Influence of Surgery Type

The impact of distal vs. proximal resection was assessed relative to risk of developing NODM. Based on the univariate analysis, there was insufficient evidence to conclude any difference in NODM following DP vs PD (HR, 1.41, 95% CI, 0.69–2.88). Incidence rates for NODM following DP vs PD were 17.5% (95% CI, 12.6–24.0%) vs 11.3% (95% CI, 5.5–22.5%) at 12 months and 24.4% (95% CI, 18.1–32.5%) vs. 11.3% (95% CI, 5.5–22.5%) at 24 months, respectively. This was further investigated with Kaplan-Meier analysis (Fig. 4, Supplemental Table 4). A log-rank test for difference in the curves for DP vs PD did not demonstrate a significant difference, including when follow-up was limited to 24 months and extended to 72 months.

DISCUSSION

In this population-based analysis of patients undergoing partial pancreatectomy for pancreatic cysts, approximately 1 in 5 patients developed NODM within 24 months following surgery. The risk of developing NODM was independently associated with increasing age, two components of metabolic syndrome (obesity and hypertension), and cardiovascular disease/heart failure, with the highest risk attributed to comorbid obesity. There was no observed difference in the risk of NODM comparing DP to PD. To our knowledge, this is the first study characterizing the risk of NODM after pancreatectomy

for PCLs and specifically among patients without any other pancreatic disease. The current study provides important information for patient counselling prior to surgery, including identifying potentially reversible contributing factors and a subset of patients who may benefit from more intensive post-operative education and follow-up.

The overall incidence of NODM following partial pancreatectomy for PCLs was 20.2% at 24 months, which is similar to other high-level studies involving resections of pancreata for combined etiologies.[19,31–34] The most recent systematic review noted a pooled estimate of NODM following PD and DP to be 16% (95% CI, 14–17%) and 21% (95% CI, 16–25%), respectively, though these data represent risk following pancreatectomy for all indications.[19] Among other recent meta-analyses in which the indication for pancreatectomy was primarily limited to benign or malignant lesions (after exclusion of chronic pancreatitis), the risk of NODM was reported to be 16% following PD and 14% following DP.[33,34] While one systematic review has reported an increased incidence of NODM after resection of malignant tumors compared with benign lesions,[32] others have not noted a difference.[8,18,33] Neoplastic classifications of PCLs follow well-defined sexual distribution patterns. Mucinous cystic neoplasms and solid pseudopapillary neoplasms are almost exclusively seen in women and are preferentially located in the body or tail of the pancreas.[35] Moreover, branch duct intraductal papillary mucinous neoplasms, which account for one-third of all PCLs, are also more common in women.[35,36] This readily explains the preponderance of females and the predominance of distal versus proximal pancreatectomies in our study.[35]

Patients aged 55–64 years were at higher risk of post-operative NODM. Age has previously been identified as a risk factor for NODM following other pancreatic insults, such as acute pancreatitis.[37–39] A retrospective review of 472 patients undergoing DP or Whipple procedure for any pancreas pathology also identified age >65 years to be a significant risk factor.[40] One potential explanation is reduced pancreatic reserve in older patients leading to increased susceptibility to sustained pancreatic dysfunction and poorer post-operative recovery. Non-diabetic components of metabolic syndrome, including hypertension and obesity, were also independent predictors of NODM. Hyperlipidemia was significant on univariate analysis and trended towards being a predictor of NODM on the multivariate analysis. Prior studies have also linked dyslipidemia and obesity to NODM following resection for various pancreatic pathologies.[10,15,16,31] The pathophysiologic relationship between cardiovascular disease/heart failure and risk of NODM illustrated in our study remains somewhat unclear. Components of metabolic syndrome including DM are implicated in cardiovascular disease, and DM displays robust relationships with both heart failure and coronary artery disease, as well as worse patient outcomes when co-prevalent.[41–43]

Distal pancreatectomy has historically been attributed to higher risk of post-operative endocrine insufficiency than PD due to the increased density of insulin-producing β-islet cells in the body and tail versus the head of the pancreas.[20,22,44] However, prior studies remain inconsistent. Our analysis did not observe a significant difference in risk of NODM following DP versus PD for PCL resection. Although there was a trend towards a higher risk in those with a DP, there is risk for a type 2 error due to the statistically small sample

size (as reflected by the wide confidence intervals). At the same time, there may be a potential biological explanation for these similarities based on our growing understanding of the hormonal regulation of metabolism. In addition to insulin, other hormones such as the incretins, gastric-inhibitor peptide (GIP) and glucagon-like peptide (GLP), play an important role glucose metabolism via intestinal stimulation of insulin secretion. GLP-1-producing L cells and GIP-producing K cells both reside primarily in the human duodenum.[45] Duodenal resection results in reduced GIP expressions and paradoxically increased GLP-1 expression from other intestinal sources, though with an overall reduction of post-prandial insulin release.[46–48] Furthermore, pancreatic polypeptide, secreted from PP cells in the ventral pancreas, plays a role in appetite suppression and weight management, which may also contribute to the risk for NODM following PD.[49,50]

In light of this, alternatives to traditional PD and DP can be considered, including central pancreatectomy, pylorus-preserving PD, and pancreatic enucleation. Most recently, however, with advancements in endoscopic ultrasound, chemo- and thermal ablative techniques using fine-needle injection or radiofrequency ablation have been developed as surgical alternatives for PCL treatment. Despite initial concern for serious adverse events, recent studies investigating ethanol-free chemoablation report reduced rates of adverse events without reduced efficacy.[51,52] Although larger trials are warranted before widespread implementation, the pooled complete resolution rate for paclitaxel based regimens is 63.9%.[53] Further, 98% of cysts achieving complete resolution retain resolution at 6-year follow up.[54] These techniques provide an exciting possibility for alternative management of PCLs, particularly in patients at high risk of post-operative complications such as those described by this study.

Several limitations should be considered when interpreting results of the current study. First, MarketScan, like other large databases, utilizes diagnostic and procedural ICD-9, ICD-10 and CPT coding, restricting which variables can be studied, and introducing risk for an unidentified confounding variable. As such, traditional risk factors for DM (eg, pre-operative hemoglobin A1c, family history of DM) could not be included, nor could other potential contributors such as ethnicity, other laboratory parameters, or volume of resected pancreas, which has previously been identified as a significant predictor of post-operative NODM.[11,17,19,55,56] Second, the database does not reveal the specific diagnosis of the resected cyst other than being diagnosed with adenocarcinoma as a peri-operative finding; and these fall within our exclusions. The final diagnosis of PCLs is confirmed histologically and may be unknown at the time of resection, reducing the real-world effect of this limitation since the purpose of this risk-profile remains primarily for pre-operative planning. Third, a significant constraint of the database is the exclusion of federally funded Medicare insurance claims. Due to this limitation, only a small fraction of adults >65 years with Medicare supplemental insurance are included in the MarketScan database and hence patient age >65 years was not a significant risk factor in this study. The other risk factors identified are expected to translate to this older age group although additional risk factors and difference in disease incidence may exist. Finally, the final sample size (n = 311) limited the statistical power of subset analyses. Consequent to this, the number of subjects with data beyond two years remains relatively small. However, stringent selection criteria were necessary to maintain a rigorous design and this sample size would be challenging

to reach using a traditional single or multicenter study design. Although not a limitation of study design, it is worth mentioning that, as post-AP screening for NODM is not routinely performed, subclinical DM cannot be captured in this study, likely resulting in an underestimate of the true incidence of NODM. Despite these considerations, such a study isolating risk of PCL resection would not be possible without the use of such a database and the results remain a valuable contribution to current practice.

In conclusion, NODM following pancreatic resection of PCLs occurs in a significant proportion of patients (20.2% at 24 months) with otherwise normal pancreata. Risk of NODM is most strongly associated with advanced age, components of metabolic syndrome (obesity and hypertension), and cardiovascular disease/heart failure. These data are informative for preoperative counselling and risk factor modification. The associated factors also identify subsets of patients who may benefit from more intensive post-operative education and follow-up as well as consideration for novel, non-surgical treatment strategies. Additional studies regarding the hormonal changes of glucose metabolism following pancreatic surgery across different disease etiologies may provide the opportunity for a more tailored approach for the patients who develop post-operative diabetes mellitus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Sources of Funding:

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Abbreviations:

ADA	American Diabetes Association
aHR	adjusted hazard ratio
AP	acute pancreatitis
ASGE	American Society for Gastrointestinal Endoscopy
CI	confidence interval
COBRA	Consolidated Omnibus Budget Reconciliation Act
CPT	Current Procedural Terminology
DM	diabetes mellitus
DP	distal pancreatectomy
GIP	gastric inhibitor peptide
GLP	glucagon-like peptide

HR	hazard ratio
ICD-9-CM	*International Classification of Diseases*, Ninth Edition Clinical Modification
ICD-10-CM	*International Classification of Diseases*, Tenth Edition Clinical Modification
NODM	new onset diabetes mellitus
PCL	pancreatic cystic lesion
PD	pancreaticoduodenectomy

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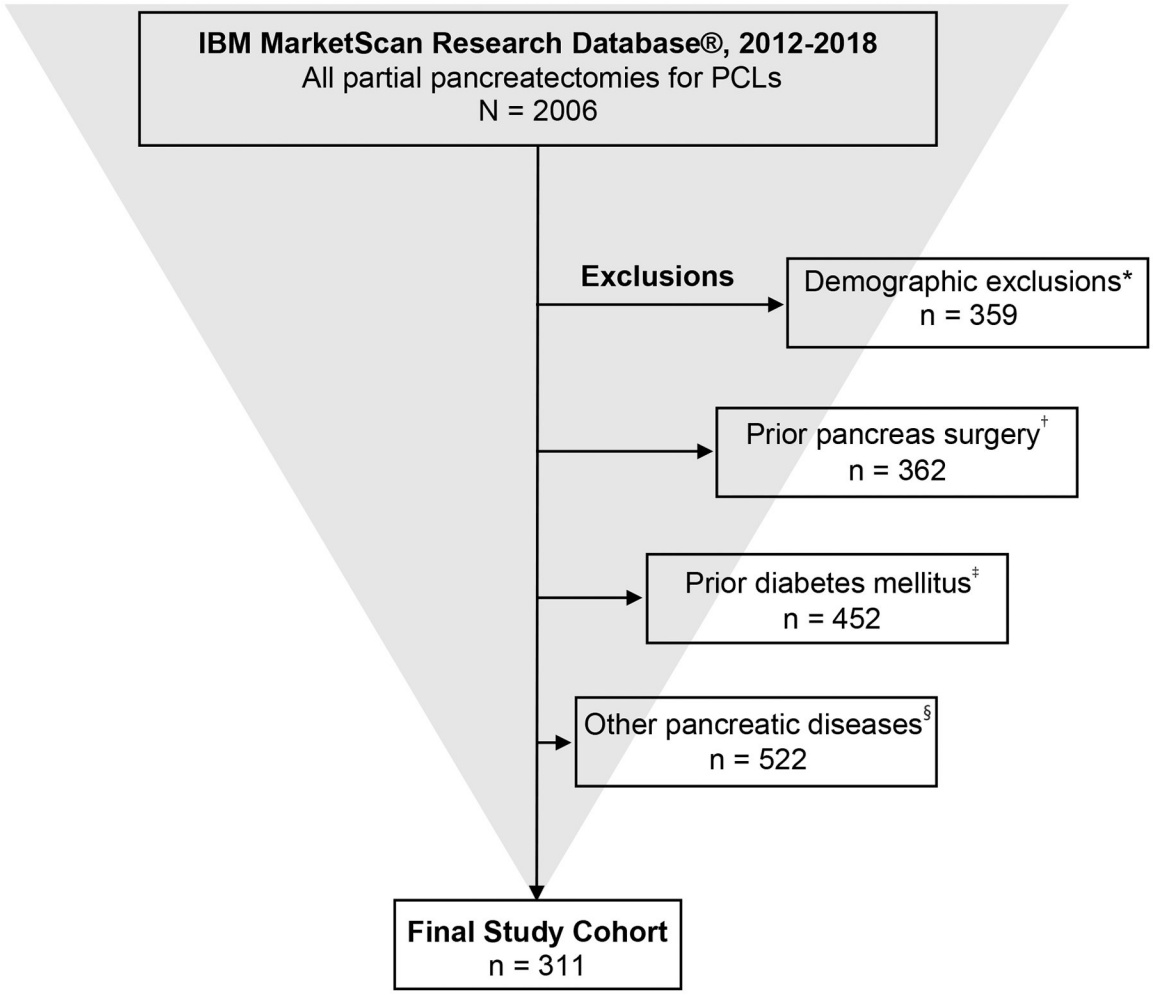

FIGURE 1.

Selection of the final study cohort. *No enrollment information, <18 years of age, <3 months pre-surgery enrollment, <1 month post-surgery enrollment, pregnancy, no data prior to surgery. †Total pancreatectomy, islet cell auto-transplantation, necrosectomy, other prior pancreas surgery. ‡Diabetes mellitus or use of anti-glycemic medications within 12 months prior to surgery. §Cystic fibrosis, hemochromatosis, prior pancreatic enzyme use, acute pancreatitis within 6 months prior to surgery, prior chronic pancreatitis, prior pancreatic cancer. PCL, pancreatic cystic lesion.

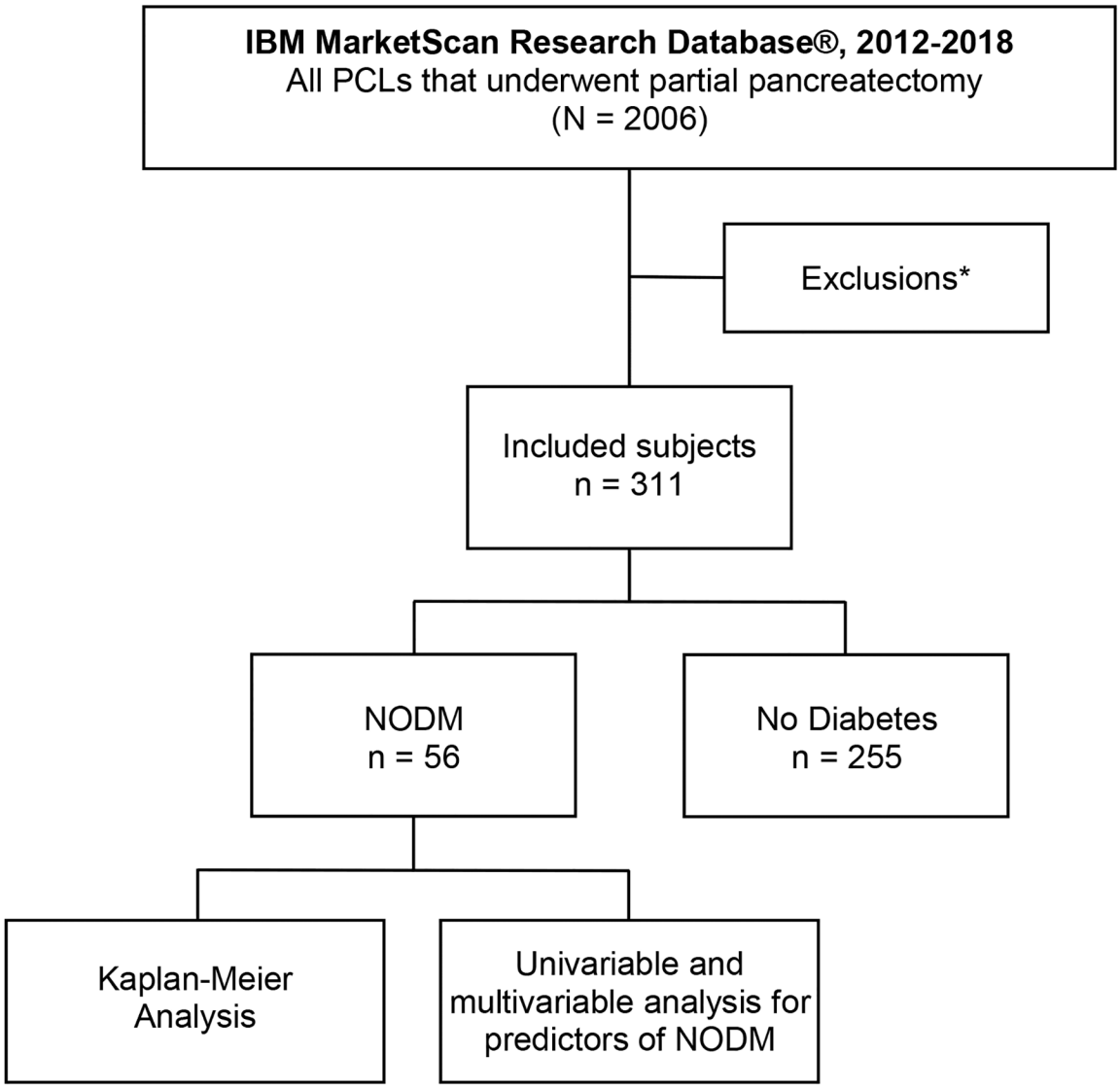

FIGURE 2.

Study flowchart. *Exclusions: No enrollment data, no prior encounters, age <18 years, <3 months prior enrollment, <1 month post-operative enrollment, total pancreatectomy, pregnancy, islet cell auto-transplantation, cystic fibrosis, hemochromatosis, pancreatic malignancy, necrosectomy, pre-existing diabetes mellitus or use of anti-glycemic medications, acute pancreatitis within 6 months, prior chronic pancreatitis, and prior pancreatic surgery. PCL, pancreatic cystic lesion; NODM, new-onset diabetes mellitus

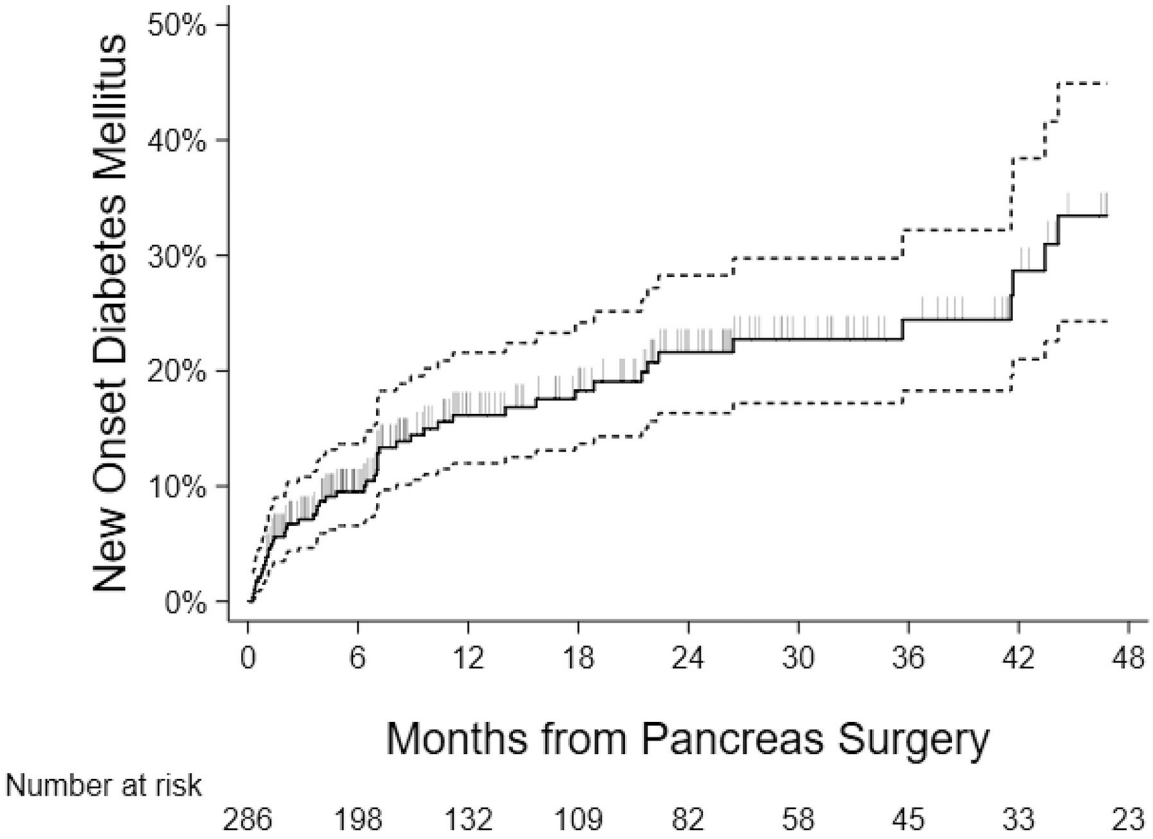

FIGURE 3.

Kaplan-Meier curve for time to NODM for patients undergoing partial pancreatectomy for PCLs: Analysis of the IBM MarketScan Research Database®, 2012–2018. Vertical slashes indicate censored observations (end of follow-up with no DM observed). Dotted lines represent the 95% confidence bands for Kaplan-Meier estimate. NODM, new-onset diabetes mellitus; PCL, pancreatic cystic lesion.

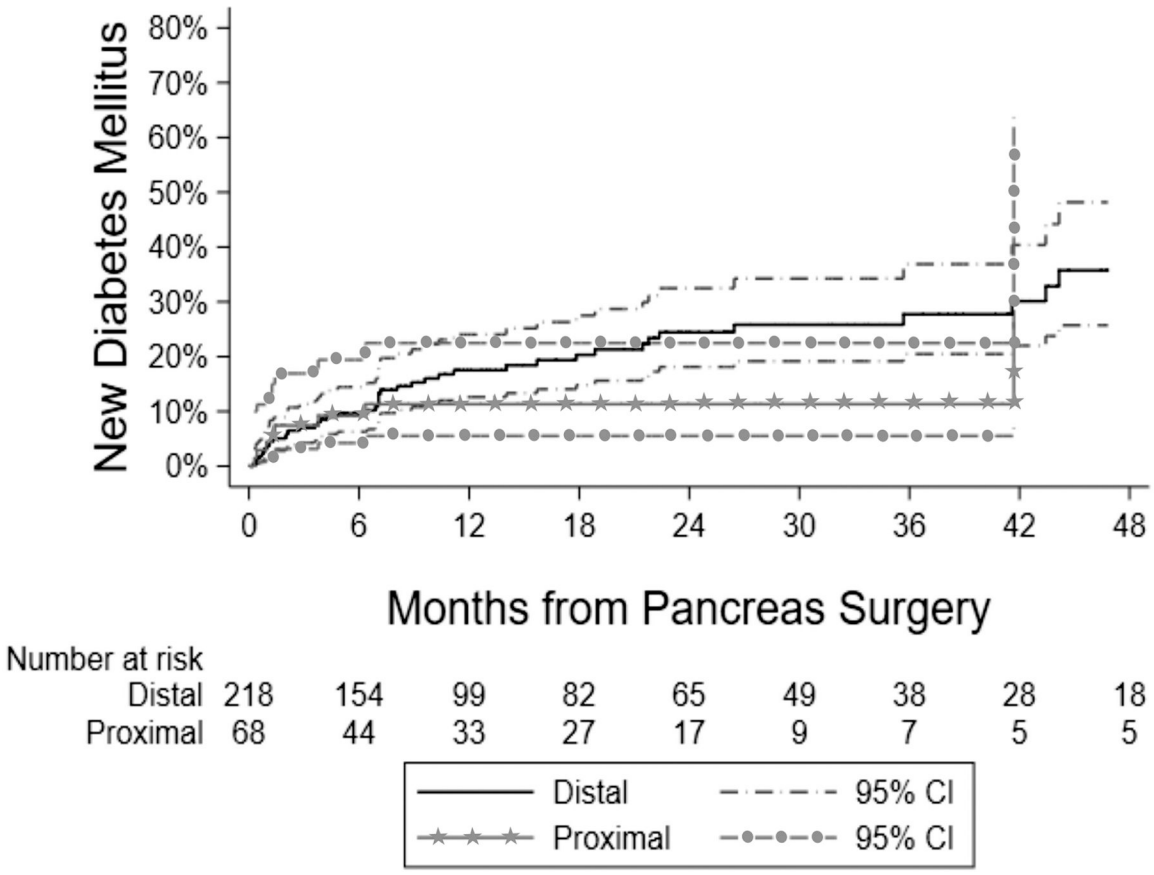

FIGURE 4.

Kaplan-Meier curve for time to NODM for patients undergoing distal compared to proximal pancreatectomy for PCLs: Analysis of the IBM MarketScan Research Database®, 2012–2018. The number at risk indicates how many patients have follow-up at that point and have not yet developed NODM. Some separation exists in the curves after 6 months up to 2, however the overlapping confidence intervals at all time points indicates no significant difference. NODM, new-onset diabetes mellitus; PCL, pancreatic cystic lesion; CI, confidence interval.

TABLE 1.

Summary of Demographics and Baseline Characteristics for all Patients who Underwent Partial Pancreatectomy for PCLs Included in the Final Cohort: Analysis of the IBM MarketScan Research Database®, 2012–2018

Variable	All PCL Surgeries (n = 311)
Age, mean (SD), y	56.2 (14.1)
Age group, y, n (%)	
18–44	63 (20.3)
45–54	69 (22.2)
55–64	102 (32.8)
65+	77 (24.8)
Sex, n (%)	
Male	74 (23.8)
Female	237 (76.2)
Region, n (%)	
Northeast	79 (25.4)
North Central	69 (22.2)
South	98 (31.5)
West	61 (19.6)
Unknown	4 (1.3)
Surgery type, n (%)	
Distal pancreatectomy	218 (70.1)
Proximal pancreatectomy	68 (21.9)
Excision of pancreatic lesion	24 (7.7)
Unspecified partial pancreatectomy	1 (0.3)
Laparoscopic surgery, n (%)	33 (10.6)
Follow up available, median (IQR), mo	16.8 (7.2–32.4)
Charlson Comorbidity Index, mean (SD)	3.4 (2.4)
Charlson Comorbidity Index ≥3, n (%)	185 (59.5)
Hypertension, n (%)	115 (37.0)
Hyperlipidemia, n (%)	51 (16.4)
Obesity, n (%)	37 (11.9)
Tobacco use, n (%)	34 (10.9)
Alcohol use, n (%)	1 (0.3)
CV disease/heart failure, n (%)	18 (5.8)
Cerebrovascular disease, n (%)	0 (0)
Chronic kidney disease, n (%)	10 (3.2)
Alcoholic liver disease, n (%)	0 (0)
Chronic hepatitis B, n (%)	0 (0)
Chronic hepatitis C, n (%)	1 (0.3)
COPD, n (%)	29 (9.3)
Depression, n (%)	14 (4.5)

PCL indicates pancreatic cystic lesion; SD, standard deviation; IQR, interquartile range; CV, cardiovascular; COPD, chronic obstructive pulmonary disease.

TABLE 2.

Time to NODM at Selected Time Points for Patients Undergoing Partial Pancreatectomy for PCLs: Analysis of the IBM MarketScan Research Database®, 2012–2018

Time Post-Surgery, mo	Estimated DM Incidence (95% CI)
3	6.9% (4.5–10.3%)
6	9.1% (6.3–12.9%)
12	15.1% (11.3–20.2%)
18	17.1% (12.8–22.6%)
24	20.2% (15.3–26.4%)
36	22.7% (17.0–29.8%)
48	32.4% (23.7–43.2%)

NODM indicates new-onset diabetes mellitus; PCL, pancreatic cystic lesion; DM, diabetes mellitus; CI, confidence interval.

TABLE 3.

Univariable Analysis and Incidence of NODM at 6, 12, and 24 Months Post-Surgery in Patients Undergoing Partial Pancreatectomy for PCLs: Analysis of the IBM MarketScan Research Database®, 2012–2018

	Incidence of New Onset Diabetes (95% CI), %				
Variable	**6 mo**	**12 mo**	**24 mo**	**Unadjusted HR (95% CI)**	***P***
Age group, y					
18–54	5.4 (2.6–11.0)	8.8 (4.8–15.9)	16.4 (9.9–26.5)	Reference	
55–64	16.7 (10.5–25.8)	26.6 (18.3–37.6)	26.6 (18.3–37.6)	2.42 (1.33–4.41)	0.004
65+	5.4 (2.1–13.7)	11.2 (5.4–22.5)	16.6 (8.7–30.5)	1.07 (0.51–2.25)	0.86
Sex					
Male	17.0 (10.0–28.1)	25.7 (16.3–39.0)	32.2 (20.8–47.6)	2.23 (1.29–3.84)	0.004
Female	6.6 (4.0–10.7)	12.0 (8.1–17.5)	16.6 (11.6–23.4)	Reference	
Region					
Northeast	8.1 (3.7–17.2)	12.1 (6.1–23.0)	14.8 (7.7–27.4)	Reference	
North Central	10.2 (5.0–20.2)	17.8 (10.2–30.1)	23.7 (14.0–38.2)	1.87 (0.86–4.07)	0.12
South	8.5 (4.3–16.3)	15.6 (9.3–25.6)	25.0 (15.7–38.3)	1.74 (0.83–3.64)	0.14
West	10.4 (4.8–21.7)	15.4 (7.9–29.0)	15.4 (7.9–29.0)	1.27 (0.52–3.07)	0.60
Unknown	n/a	n/a	n/a	n/a	n/a
Surgery type					
Distal pancreatectomy	9.6 (6.3–14.5)	17.5 (12.6–24.0)	24.4 (18.1–32.5)	1.41 (0.69–2.88)	0.35
Proximal pancreatectomy	9.2 (4.2–19.4)	11.3 (5.5–22.5)	11.3 (5.5–22.5)	Reference	
Excision of pancreatic lesion	4.2 (0.6–26.1)	4.2 (0.6–26.1)	4.2 (0.6–26.1)	0.25 (0.03–1.95)	0.18
Unspecified partial pancreatectomy	n/a	n/a	n/a	n/a	n/a
Laparoscopic surgery	9.5 (3.2–26.7)	9.5 (3.2–26.7)	9.5 (3.2–26.7)	0.66 (0.21–2.12)	0.49
Open surgery	9.0 (6.1–13.1)	15.6 (11.5–21.0)	20.9 (15.7–27.5)		
Charlson comorbidity index				1.78 (1.01–3.15)	0.05
<3	4.9 (2.2–10.6)	8.5 (4.4–15.8)	15.4 (8.9–25.9)		
≥3	11.9 (7.9–17.7)	19.8 (14.2–27.1)	23.4 (17.0–31.8)		
Hypertension				2.23 (1.31–3.79)	0.003
Present	14.4 (9.1–22.5)	20.9 (14.0–30.5)	29.1 (20.0–41.3)		
Absent	5.9 (3.3–10.4)	11.7 (7.6–17.9)	15.1 (10.0–22.5)		
Hyperlipidemia				1.90 (0.99–3.63)	0.05
Present	12.5 (5.8–25.8)	25.0 (14.0–42.2)	35.1 (20.5–55.7)		
Absent	8.4 (5.5–12.6)	13.5 (9.5–18.8)	17.6 (12.7–24.1)		
Obesity				2.32 (1.22–4.42)	0.01
Present	17.0 (8.0–34.0)	27.5 (15.2–46.6)	31.8 (18.2–51.6)		
Absent	8.0 (5.3–12.0)	13.4 (9.5–18.6)	18.5 (13.4–25.2)		
Tobacco use				1.03 (0.41–2.60)	0.94
Present	6.3 (1.6–23.0)	20.3 (8.8–42.9)	20.3 (8.8–42.9)		
Absent	9.4 (6.4–13.6)	14.6 (10.7–19.9)	20.1 (15.0–26.7)		
CV disease/heart failure				2.33 (0.99–5.46)	0.05
Present	22.2 (9.0–48.9)	22.2 (9.0–48.9)	22.2 (9.0–48.9)		

	Incidence of New Onset Diabetes (95% CI), %				
Variable	**6 mo**	**12 mo**	**24 mo**	**Unadjusted HR (95% CI)**	***P***
Absent	8.2 (5.5–12.1)	14.6 (10.7–19.8)	19.9 (14.9–26.3)		
Chronic kidney disease				0.58 (0.08–4.21)	0.59
Present	0	12.5 (1.9–61.3)	12.5 (1.9–61.3)		
Absent	9.3 (6.5–13.3)	15.2 (11.3–20.4)	20.4 (15.4–26.7)		
COPD				1.02 (0.41–2.57)	0.96
Present	10.7 (3.6–29.8)	19.7 (8.6–41.3)	19.7 (8.6–41.3)		
Absent	8.8 (6.0–12.9)	14.6 (10.6–19.9)	20.1 (14.9–26.7)		
Depression				0.78 (0.19–3.21)	0.73
Present	7.1 (1.0–40.9)	7.1 (1.0–40.9)	22.6 (5.5–68.5)		
Absent	9.1 (6.3–13.1)	15.5 (11.5–20.7)	19.9 (15.0–26.2)		

Incidence rates are derived from the Kaplan-Meier Estimator except the Charlson Index, which is derived from the Cox proportional hazard model as it was modeled as a continuous variable. Hazard ratios are from univariable Cox proportional hazards models for time to NODM. Variables with very low counts were excluded to avoid unintentional identification of individual patients.

NODM indicates new-onset diabetes mellitus; n/a, not applicable; PCL, pancreatic cystic lesion; CI, confidence interval; CV, cardiovascular; COPD, chronic obstructive pulmonary disease.

TABLE 4.

Multivariable Cox Proportional Hazard Model for Time to NODM in Patients Undergoing Partial Pancreatectomy for PCLs: Analysis of the IBM MarketScan Research Database®, 2012–2018

Variable	Adjusted Hazard Ratio (95% CI)	*P*
Age, y		
18–54	Reference	
55–64	1.97 (1.04–3.72)	0.04
65+	0.74 (0.33–1.62)	0.44
Sex, male vs female	1.62 (0.91–2.88)	0.10
Obesity vs no	2.63 (1.35–5.12)	0.004
Hypertension vs no	1.79 (1.01–3.17)	0.04
CV disease/heart failure vs no	2.54 (1.02–6.28)	0.04

Backward selection with inclusion criteria $P \leq 0.05$ was used to select the final multivariable model. Candidates for the multivariable model included age, sex, region, surgery type, hypertension, hyperlipidemia, obesity, and cardiovascular disease/heart failure. Variables with $P < 0.01$ in univariable modeling were kept in the multivariable model regardless of *P*. All two-way interactions were tested.

NODM indicates new-onset diabetes mellitus; PCL, pancreatic cystic lesion, CI, confidence interval; CV, cardiovascular.