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AUTHOR(S):

Yamamoto-Kataoka, Sachiko; Shimizu, Sayaka; Yamazaki, Hajime; Murakami, Katsuhiro; Nishizaki, Daisuke; Fukuhara, Shunichi; Inagaki, Nobuya; Yamamoto, Yosuke

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# Development of a preoperative prediction model for new-onset diabetes mellitus after partial pancreatectomy

## A retrospective cohort study

Sachiko Yamamoto-Kataoka, MD, MPH, PhD<sup>a</sup>, Sayaka Shimizu, MD, PhD<sup>a,b</sup>, Hajime Yamazaki, MD, PhD<sup>a,b</sup>, Katsuhiko Murakami, MD, PhD<sup>c</sup>, Daisuke Nishizaki, MD<sup>c</sup>, Shunichi Fukuhara, MD, PhD<sup>a,b,d</sup>, Nobuya Inagaki, MD, PhD<sup>e</sup>, Yosuke Yamamoto, MD, PhD<sup>a,\*</sup> 

### Abstract

Pancreatectomy is an invasive surgery that is sometimes associated with complications. New-onset diabetes mellitus sometimes develops after partial pancreatectomy and severely affects the patient's quality of life. This study aimed to develop a preoperative prediction model of new-onset diabetes mellitus after partial pancreatectomy, which will help patients and surgeons to achieve more easily better common decisions on regarding whether to perform partial pancreatectomy. This retrospective cohort study analyzed medical records of patients who underwent partial pancreatectomy (total pancreatectomy excluded) from April 1, 2008, to February 28, 2016, which were available in the database provided by Medical Data Vision Co., Ltd. (Tokyo, Japan). The predictors were preoperative age, body mass index, hemoglobin A1c level, blood glucose level, and indication for partial pancreatectomy. The outcome was the development of new-onset diabetes mellitus at 1 to 12 months after partial pancreatectomy. We used a logistic regression model and calculated the scores of each predictor. To determine test performance, we assessed discrimination ability using the receiver operating characteristic curve and calibration with a calibration plot and the Hosmer-Lemeshow test. We also performed internal validation using the bootstrap method. Of 681 patients, 125 (18.4%) had new-onset diabetes mellitus after partial pancreatectomy. The developed prediction model had a possible range of 0 to 46 points. The median score was 13, and the interquartile range was 9 to 22. The C-statistics of the receiver operating characteristic curve on the score to predict the outcome was .70 (95% confidence interval [CI], .65–.75). Regarding the test performance, the Hosmer-Lemeshow test was not significant ( $P = .17$ ), and calibration was good. In the bootstrapped cohorts, the C-statistics was .69 (95% CI, .62–.76). We developed a preoperative prediction model for new-onset diabetes mellitus after partial pancreatectomy. This would provide important information for surgeons and patients when deciding whether to perform partial pancreatectomy.

**Abbreviations:** CI = confidence interval, D-bil = direct bilirubin, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, IQR = interquartile range, LDL-C = low-density lipoprotein cholesterol, NET = neuroendocrine tumor, PT = prothrombin activity, PT-INR = international normalized ratio of prothrombin time, T-bil = total bilirubin.

**Keywords:** new-onset diabetes mellitus, partial pancreatectomy, prediction model

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

<sup>a</sup>Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, <sup>b</sup>Section of Clinical Epidemiology, Department of Community Medicine, <sup>c</sup>Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto City, Kyoto, <sup>d</sup>Center for Innovative Research for Communities and Clinical Excellence, Fukushima Medical University, Fukushima City, Fukushima, <sup>e</sup>Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto City, Kyoto, Japan.

\*Correspondence: Yosuke Yamamoto, Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto City, Kyoto, Japan (e-mail: [yamamoto.yosuke.5n@kyoto-u.ac.jp](mailto:yamamoto.yosuke.5n@kyoto-u.ac.jp)).

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## 1. Introduction

Pancreatectomy is an invasive surgery that can be accompanied by severe complications.<sup>[1]</sup> Therefore, there is a need for shared decision-making among patients and surgeons regarding pancreatectomy, considering both the benefits and the risks of complications. Pancreatic tumors, which are not diagnosed as malignant tumors, can be resected to diagnose or prevent malignant transformation.<sup>[2,3]</sup> In such cases, the benefit from pancreatectomy could be less clear than that in cases of malignant tumors. Whether the tumor is malignant or not, information about complications could be important for shared decision-making.

Diabetes mellitus develops due to relative or absolute insulin deficiency.<sup>[4]</sup> Insulin is the only hormone produced in the islet beta cells of the pancreas, and it controls blood glucose levels. Therefore, new-onset diabetes mellitus develops after total pancreatectomy.<sup>[5]</sup> In contrast, new-onset diabetes mellitus does not always develop when partial resection of the pancreas is performed. In previous reports, 4% to 39% of patients who underwent pancreatectomy, except total pancreatectomy, developed new-onset diabetes mellitus.<sup>[6–8]</sup>

Patients with diabetes mellitus are at risk for various life-threatening complications, including cardiovascular diseases. Moreover, these complications as well as microvascular complications worsen their quality of life and could increase medical costs.<sup>[9,10]</sup> Therefore, for surgeons, a preoperative prediction model to identify patients with a higher risk of new-onset diabetes mellitus after partial pancreatectomy will be useful in real-life clinical settings.

Clinical factors such as age, preoperative hemoglobin A1c (HbA1c) level, fasting blood glucose level, and body mass index (BMI) and operation-related factors, such as resected and remnant pancreatic volume, were suggested as predictors of new-onset diabetes mellitus after pancreatectomy.<sup>[11–14]</sup> A previous study developed postoperative prediction models for new-onset diabetes mellitus after pancreaticoduodenectomy.<sup>[12]</sup> However, no preoperative prediction model that would be more useful for improved shared decision-making regarding whether to perform partial pancreatectomy has been reported.

Therefore, this study aimed to develop a preoperative prediction model for new-onset diabetes mellitus after partial pancreatectomy.

## 2. Methods

### 2.1. Study design, setting, and participants

This was a retrospective cohort study. We used anonymous data from the database provided by Medical Data Vision Co., Ltd. (Tokyo, Japan). The database consists of diagnostic procedure combination data, national administrative claims, laboratory data, and a discharge database of inpatients.<sup>[15]</sup> The data were derived from 245 hospitals, which accounted for 15.5% of hospitals that used the diagnostic procedure combination fixed-payment reimbursement system. Of the 245 hospitals, 33 provided laboratory data. A total of 14,160,000 patients from 245 hospitals were registered in the database.

The study participants were patients who underwent partial pancreatectomy (total pancreatectomy excluded) between April 1, 2008, and February 28, 2016. Patients with preoperative diabetes mellitus were excluded from the study. Preoperative diabetes mellitus was diagnosed from the data and records within 3 months before partial pancreatectomy. Preoperative diabetes

mellitus was defined as having a blood glucose level  $\geq 200$  mg/dL at least twice, an HbA1c level  $\geq 6.5\%$  once, or a record of the code of diabetes mellitus and use of a hypoglycemic drug before partial pancreatectomy in the database. Therefore, the preoperative HbA1c level of the subjects included in this study was  $\leq 6.4\%$  and the blood glucose level was  $< 200$  or  $\geq 200$  mg/dL only once.

We defined the code for diabetes mellitus as E10–14 in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes. Patients who underwent partial pancreatectomy more than twice between April 1, 2008, and February 28, 2016, had a neuroendocrine tumor (NET), or had missing data of predictors were also excluded. ICD-10 codes for NET were identified in C16.9, 17.0/9, 22.9, 23, 25.0/4, 26.9, 80, D13.7, 37.2/7/9, or E34.0 by an endocrinologist. The observation period was set at 1 to 12 months after partial pancreatectomy to exclude the period of unstable glucose metabolism immediately after surgery,<sup>[16]</sup> and based on previous studies suggesting that most new-onset diabetes develops within 1 year.<sup>[17,18]</sup>

### 2.2. Outcome

The outcome was identified as new-onset diabetes mellitus, which developed 1 to 12 months after partial pancreatectomy. New-onset diabetes mellitus was identified when at least one of the 3 criteria was met in the observation period: (1) blood glucose level  $\geq 200$  mg/dL at least twice, (2) HbA1c level  $\geq 6.5\%$  once, or (3) ICD-10 code for diabetes mellitus and use of a hypoglycemic drug. Data on antihyperglycemic medications prescribed within 3 months prior to the last visit during the observation period were also extracted from the database.

### 2.3. Predictors

We selected 5 preoperative predictors from previous reports and clinical perspectives.<sup>[11–13]</sup> The predictors were age, BMI, HbA1c level, blood glucose level, and indication for partial pancreatectomy, which were all measured preoperatively. Age was measured at the time of the last visit before partial pancreatectomy. BMI was calculated from the data of height and weight upon admission for partial pancreatectomy. For laboratory data, the last data obtained within 3 months before partial pancreatectomy were used. Indications for partial pancreatectomy were selected depending on the disease codes from the database by 2 surgeons independently. Disagreements were resolved by discussion between the 2 surgeons and 1 gastroenterologist. Finally, the ICD-10 codes C16.1–6/9, 17.0/9, 22.1/7/9, 23, 24.0–1/9, 25.0–3/7–9, 26.1, D01.4, D13.5–6, D37.2/6–7, K318, and K86.0–2/8–9, excluding NET, were defined as indications for partial pancreatectomy. These codes of indications for partial pancreatectomy were categorized into 5 groups: pancreatic malignant tumor, malignant tumor in other organs, benign tumor, chronic pancreatitis, and others. When the patient had the disease codes from more than 2 categories, 1 indication was selected according to the following criteria: (1) pancreatic malignant tumor, (2) malignant tumor in other organs, (3) benign tumor, (4) chronic pancreatitis, and (5) others.

### 2.4. Other patient characteristics

To describe patient characteristics, we collected information on sex, history of acute and chronic pancreatitis, and preoperative

laboratory data of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, amylase, albumin, total bilirubin (T-bil), and direct bilirubin (D-bil) levels, prothrombin activity (PT), and international normalized ratio of prothrombin time (PTINR). Acute and chronic pancreatitis was defined as ICD-10 codes K85, K860, and K861 from the ICD-10 codes from records that existed within 3 months before partial pancreatectomy with the data of their diagnosis dates.

## 2.5. Statistical analysis

Continuous variables were summarized as medians and interquartile ranges (IQRs), and categorical data as numbers and percentages (%). For the univariate analysis, we used the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. A *P* value of less than .05 indicated statistical significance.

In the derivation of the prediction model, a logistic regression model was used to estimate the probability of developing new-onset diabetes. Regarding predictors of continuous variables, we categorized them by cutoff values, which were defined from previous reports and clinical significance to facilitate the use of the prediction model. We classified age into 2 categories (<60, ≥60 years), BMI into 3 categories (<18.5, ≥18.5 and <25, and ≥25 kg/m<sup>2</sup>), HbA1c level into 4 categories (<5.0%, ≥5.0% and <5.5%, ≥5.5% and <6.0%, and ≥6.0% and <6.5%),<sup>[19]</sup> and blood glucose level into 2 categories (<200 and ≥200 mg/dL). A regression coefficient-based scoring method was used to calculate the scores for each predictor. We divided each beta coefficient with the smallest beta coefficient and rounded it to the nearest integer. The scores for each variable were summed to obtain the total scores. Regarding test performance, the discrimination ability was assessed using the receiver operating characteristic (ROC) curve and C-statistics. We assessed the calibration ability with a calibration plot, comparing the predicted probabilities with the prevalence of new-onset diabetes mellitus and the Hosmer-Lemeshow test. For internal validation to assess the optimism of discrimination ability, the bootstrap method was used, where 500 bootstrapped datasets were created and C-statistics were calculated. We performed a complete case analysis. All statistical analyses were performed using STATA version 14.2 (Stata Corp., College Station, TX, USA).

## 2.6. Ethical consideration

This study was approved by the Ethics Committees of Kyoto University Graduate School and Faculty of Medicine (R1232). Informed patient consent was not required as we used anonymized data in this retrospective study.

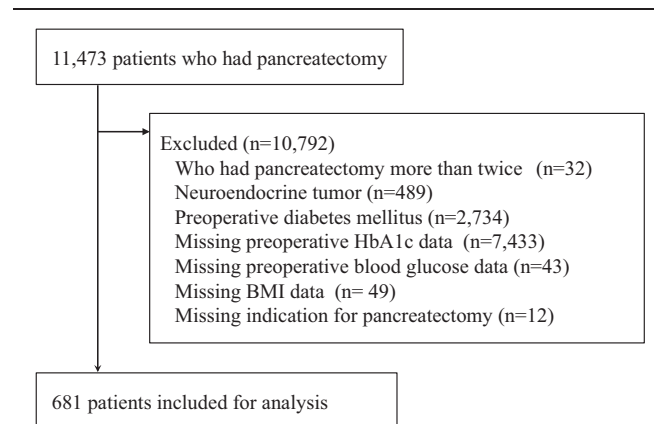
## 3. Results

### 3.1. Study flow diagram

We identified 11,473 patients in the database who underwent partial pancreatectomy, and 681 patients who met the eligibility criteria were included (Fig. 1).

### 3.2. Patient characteristics

The median age was 70 years (IQR, 63–77), and 58.9% of patients were male. As shown in Table 1, new-onset diabetes mellitus developed in 125 patients (18.4%) after partial



**Figure 1.** Flowchart of patient selection. BMI=body mass index, HbA1c=hemoglobin A1c.

pancreatectomy. Sixty-one patients with new-onset diabetes mellitus were treated with hypoglycemic drugs (Supplemental Table 1, <http://links.lww.com/MD/G196>, which demonstrates antihyperglycemic medications among patients with new-onset diabetes mellitus). Comparing the data of patients with and without new-onset diabetes mellitus, there was no significant difference in age; sex; past histories of acute or chronic pancreatitis; total cholesterol, HDL-C, LDL-C, amylase, albumin, T-bil, or D-bil levels; PT; PT-INR; or indications for partial pancreatectomy except pancreatic malignant tumor. BMI, HbA1c, blood glucose, and triglyceride levels, and the prevalence of pancreatic malignant tumors were higher in patients with new-onset diabetes mellitus than in those without new-onset diabetes mellitus.

### 3.3. Development and internal validation of the prediction model

Table 2 shows the results of multivariable analysis and the score of the prediction model. The possible range of the total score was 0 to 46.

The distribution of the scores is shown in Figure 2. The median score was 13, and the IQR was 9 to 22. The risk scores and observed and predicted development of new-onset diabetes mellitus are shown in Table 3. Scores were divided into 4 categories (0–9, 10–19, 20–29, and ≥30), and as scores increased, the observed and predicted development of new-onset diabetes mellitus also increased. The range of observed new-onset diabetes mellitus was 6.7% to 45.5% and that of predicted new-onset diabetes mellitus was 8.1% (IQR, 7.4–10.3) to 43.4% (IQR, 43.4–43.4), as shown in Table 3. Regarding discrimination ability, the ROC curve is shown in Figure 3, and the C-statistics was .70 (95% confidence interval [CI], .65–.75). Regarding calibration, the calibration plot showed that the predicted probability had a good fit for the observed probability (Fig. 4). The Hosmer-Lemeshow test was not significant (*P*=.17). The internal validation with the 500 bootstrapped datasets showed a C-statistics of .69 (95% CI, .62–.76).

## 4. Discussion

We developed a preoperative prediction model for new-onset diabetes mellitus after partial pancreatectomy using data from

**Table 1**

**Baseline characteristics of the participants.**

	Total n = 681	DM (-) n = 556	DM (+) n = 125	P value
Age (yr)	70 (63–77)	70 (63–77)	71 (63–77)	.48
Male (sex)	401 (58.9)	330 (59.4)	71 (56.8)	.62
BMI (kg/m <sup>2</sup> )	21.8 (20.0–23.8)	21.7 (19.9–23.8)	22.4 (20.7–24.6)	.03
Indication for pancreatotomy				
Pancreatic malignant tumor	374 (54.9)	295 (53.1)	79 (63.2)	.05
Malignant tumor in other organs	233 (34.2)	198 (35.6)	35 (28.0)	.12
Benign tumor	65 (9.5)	56 (10.1)	9 (7.2)	.40
Chronic pancreatitis	7 (1.0)	6 (1.1)	1 (.8)	1.00
Others	2 (.3)	1 (.2)	1 (.8)	.33
Past history				
Acute pancreatitis	144 (21.1)	119 (21.4)	25 (20.0)	.81
Chronic pancreatitis	54 (7.9)	45 (8.1)	9 (7.2)	.86
HbA1c (%)	5.7 (5.4–6.0)	5.6 (5.4–5.9)	6.0 (5.7–6.2)	<.001
Glucose (mg/dL)	110 (98–129)	109 (97–127)	115 (101–137)	.01
Total cholesterol (mg/dL)	184 (158–216)	184 (158–216)	185 (160–219)	.41
Missing	137	120	17	
HDL-C (mg/dL)	50 (37–64)	50 (37–64)	50 (40–65)	1.00
Missing	407	335	72	
LDL-C (mg/dL)	105 (86–129)	105 (87–128)	105 (86–134)	.87
Missing	466	386	80	
Triglyceride (mg/dL)	101 (74–147)	96 (73–142)	122 (76–157)	.01
Missing	197	174	23	
Amylase (U/L)	117 (79–200)	118 (79–197)	105 (70–226)	.65
Missing	16	13	3	
Albumin (g/dL)	3.2 (2.6–4.0)	3.2 (2.6–4.0)	3.2 (2.6–4.0)	.57
Missing	2	2	0	
T-bil (mg/dL)	.83 (.60–1.40)	.90 (.60–1.42)	.80 (.60–1.14)	.09
Missing	2	2	0	
D-bil (mg/dL)	.22 (.10–.60)	.205 (.10–.60)	.30 (.10–.50)	.83
Missing	58	44	14	
PT (%)	95.0 (83.9–105.0)	95.0 (83.9–105.0)	95.5 (84.5–105.8)	.89
Missing	182	134	48	
PTINR	1.01 (.96–1.08)	1.01 (.96–1.08)	1.01 (.97–1.06)	.30
Missing	0	0	0	

Data are presented as median (interquartile range) for continuous measures and as percentage for categorical measures.

BMI=body mass index, D-bil=direct bilirubin, DM=new-onset diabetes mellitus, HbA1c=hemoglobin A1c, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, PT=prothrombin activity, PTINR=international normalized ratio of prothrombin time, T-bil=total bilirubin.

**Table 2**

**Score of each predictor for estimating the occurrence of new-onset diabetes mellitus after pancreatotomy.**

	Beta	Odds ratio (95% CI)	P value	Score
Age (yr)				
<60	.14	1.15 (.65–2.05)	.62	2
≥60	Reference	–	–	0
BMI (kg/m <sup>2</sup> )				
<18.5	Reference	–	–	0
18.5 to <25	.33	1.39 (.71–2.73)	.34	4
≥25	.71	2.03 (.93–4.43)	.08	8
HbA1c (%)				
<5.0	.41	1.51 (.50–4.57)	.46	5
5.0 to <5.5	Reference	–	–	0
5.5 to <6.0	.46	1.58 (.81–3.09)	.18	5
6.0 to <6.5	1.61	5.02 (2.61–9.66)	<.001	18
Blood glucose (mg/dL)				
<200	Reference	–	–	0
≥200	.26	1.30 (.39–4.39)	.67	3
Indication for pancreatotomy				
Pancreatic malignant tumor	.40	1.50 (.68–3.29)	.32	4
Malignant tumor in other organs	.09	1.10 (.47–2.57)	.83	1
Benign tumor	Reference	–	–	0
Chronic pancreatitis	.14	1.15 (.11–11.73)	.91	2
Others	1.34	3.80 (.20–72.13)	.37	15

95% CI=95% confidence interval, BMI=body mass index, HbA1c=hemoglobin A1c.



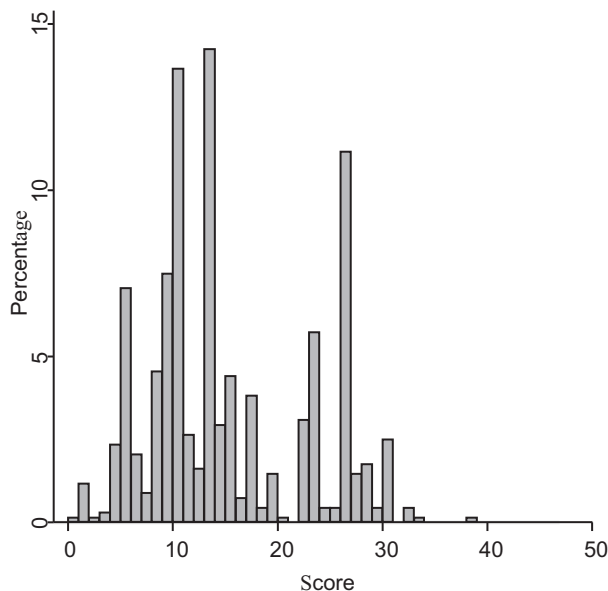


Figure 2. Distribution of patients with new-onset diabetes mellitus.

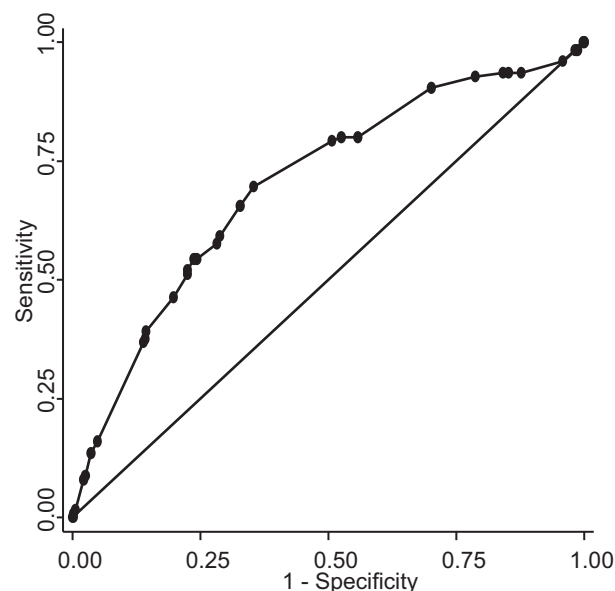


Figure 3. Receiver operating characteristic curve of the prediction model, showing a C-index of .70 (95% confidence interval, .65–.75).

681 patients in Japan. Diabetes mellitus developed in 125 patients (18.4%). The scores from this model had a possible range of 0 to 46 and a C-index of .70 (95% CI, .65–.75), which was similar to the result of internal validation using the bootstrapped method, indicating good calibration.

To the best of our knowledge, this is the first report of a preoperative prediction model of new-onset diabetes mellitus after partial pancreatectomy. Previous studies have suggested an association between new-onset diabetes mellitus and preoperative factors related to glucose intolerance, such as increased fasting blood glucose level, HbA1c level, and BMI.<sup>[12–14]</sup> In this study, the highest HbA1c level (>6.0%) was significantly associated with the development of new-onset diabetes mellitus. Unexpectedly, the point estimate of odds ratio was higher in the lowest preoperative HbA1c level category (<5.0%) than in the second lowest category (≥5.0%, <5.5%). One possible reason is that patients with malignant tumors are likely to present anemia with many mechanisms, which might lead to the underestimation of glycemic control based on HbA1c level.<sup>[20,21]</sup> In fact, the proportion of malignant tumors as an indication for partial pancreatectomy was the highest in the HbA1c level <5.0% group (95.0%, 86.8%, 87.8%, and 91.8% in HbA1c levels <5.0%, 5.0%–5.5%, 5.5%–6.0%, and >6.0% but <6.5%, respectively), and median [IQR] hemoglobin level was lowest in the HbA1c

<5.0% group (11.4 [10.0–12.6] g/dL, 12.6 [11.3–13.6] g/dL, 13.2 [12.2–14.4] g/dL, and 13.0 [12.0–14.1] g/dL in <5.0%, 5.0%–5.5%, 5.5%–6.0%, and >6.0% but <6.5%, respectively), supporting the assumed mechanism. Regarding the score for age, it was also unexpected that a lower score would be calculated for the elderly (age ≥60 years) than for the younger group. A

**Table 3**  
Risk score and observed and predicted occurrence of new-onset diabetes mellitus.

Score	Number (%) total n=681	Observed DM (%)	Predicted DM, %, median (IQR)
0–9	178 (26.1)	12 (6.7)	8.1 (7.4–10.3)
10–19	313 (46.0)	48 (15.3)	14.2 (11.2–15.3)
20–29	168 (24.7)	55 (32.7)	34.8 (29.0–34.8)
≥30	22 (3.2)	10 (45.5)	43.4 (43.4–43.4)

DM=new-onset diabetes mellitus, IQR=interquartile range.

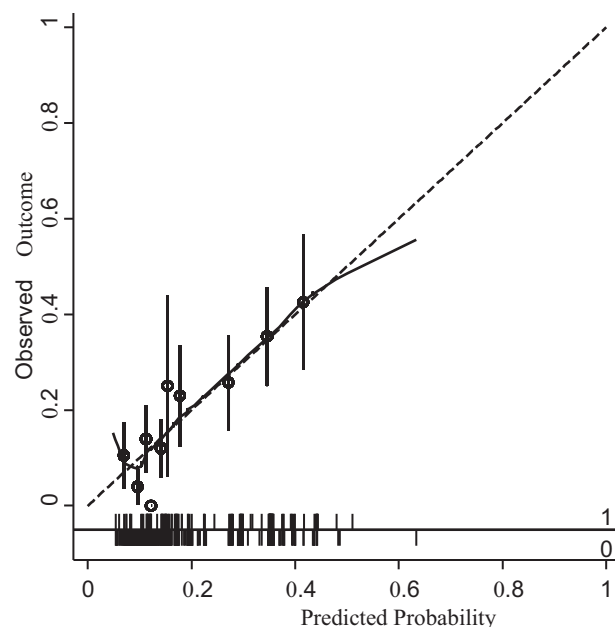


Figure 4. Calibration plot for the prediction model. The solid curve shows the predicted probabilities. The dotted line shows perfect fitting. The solid vertical line shows the number of data points for each predicted probability; 0 indicates that new-onset diabetes mellitus did not occur and 1 indicates the development of new-onset diabetes.

previous prospective cohort study of patients who underwent pancreatectomy suggested that older age was a risk factor for new-onset diabetes.<sup>[11]</sup> The study excluded patients with malignancy, while approximately 90% of patients had malignancy in this study. One possible explanation is that older patients with glucose intolerance and malignancy might tend to develop diabetes mellitus preoperatively and were therefore excluded from our study.<sup>[22]</sup> The mean age of patients who already had diabetes before surgery and were excluded from the analysis was 70.4 years (SD 8.2), which was higher than the lower limit of 60 years and may, therefore, support this hypothesis.

In a previous study, a postoperative prediction model for new-onset diabetes modeled after pancreaticoduodenectomy with a retrospective cohort was developed.<sup>[12]</sup> The postoperative model included preoperative impaired glucose tolerance, preoperative fasting blood glucose level, and resected specimen length of the pancreas as predictors, and the discrimination ability was high (C-index, .84). Another study suggested that the proportion of pancreatic volume reduction at 6 months after pancreaticoduodenectomy predicted new-onset diabetes mellitus or impaired glucose tolerance with high discrimination ability (C-index, .85).<sup>[14]</sup> However, prediction models that include postoperative factors are difficult to use preoperatively. The prediction model developed in this study consisted of only preoperative predictors and could be used before partial pancreatectomy. This would contribute to shared treatment decisions on partial pancreatectomy between patients and surgeons with the prediction of new-onset diabetes mellitus using Tables 2 and 3 and earlier diagnosis of new-onset diabetes mellitus, leading to the prevention of severe conditions such as cardiovascular or microvascular diseases.

This study has several strengths. First, the total score of this prediction model can be calculated by summing the simple integer scores. This contributes to its use in clinical settings. Second, internal validation using the bootstrap method was performed to evaluate the optimism of the model. Third, the sample size was relatively large.

There are several limitations to this study. First, misclassification of the disease based on the disease codes could have occurred because the database was derived from the claims data and did not aim to reflect all patients' comorbidities. To improve the validity of the outcomes, diabetes mellitus was defined by both disease codes and the use of hypoglycemic drugs. Second, because only casual blood glucose data were available in the database, the criteria for the fasting blood glucose level could not be set when defining diabetes mellitus. Therefore, the development of diabetes mellitus might have been under- or overestimated due to this misclassification. Third, new-onset diabetes mellitus could be missed if postoperative blood glucose or HbA1c levels were not measured or if patients were diagnosed and prescribed hypoglycemic drugs by other clinics or hospitals. This leads to an underestimation of the development of diabetes mellitus. However, the prevalence of new-onset diabetes mellitus in this study was similar to that reported in previous studies,<sup>[6–8]</sup> and a large proportion of patients in the database had missing data, especially preoperative HbA1c levels, and were excluded from the study. This is mainly because laboratory data from 212 hospitals were not registered in the database, potentially due to patients' or physicians' preferences. Fifth, a planned surgical procedure was not available in this study. Previous studies have shown that the type of surgical procedure can be an important predictor of new-onset diabetes.<sup>[6–8]</sup> Adding the planned surgical procedure to the model may improve the predictive ability of the

model. Lastly, external validation was not performed because the sample size was relatively small for the derivation and validation cohorts. In this regard, further studies are needed.

## 5. Conclusion

We developed a preoperative prediction model for new-onset diabetes mellitus after partial pancreatectomy. This model can help surgeons and patients achieve better common decisions on whether to perform partial pancreatectomy. Further external validation studies are needed.

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## Author contributions

**Conceptualization:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Hajime Yamazaki, Yosuke Yamamoto.

**Data curation:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Yosuke Yamamoto.

**Formal analysis:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Yosuke Yamamoto.

**Investigation:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Yosuke Yamamoto.

**Methodology:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Hajime Yamazaki, Katsuhiro Murakami, Daisuke Nishizaki, Yosuke Yamamoto.

**Project administration:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Shunichi Fukuhara, Yosuke Yamamoto.

**Resources:** Sachiko Yamamoto Kataoka, Yosuke Yamamoto.

**Software:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Yosuke Yamamoto.

**Supervision:** Nobuya Inagaki, Yosuke Yamamoto, Shunichi Fukuhara.

**Validation:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Yosuke Yamamoto.

**Visualization:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Yosuke Yamamoto.

**Writing – original draft:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Yosuke Yamamoto.

**Writing – review & editing:** Sachiko Yamamoto Kataoka, Sayaka Shimizu, Hajime Yamazaki, Katsuhiro Murakami, Daisuke Nishizaki, Shunichi Fukuhara, Nobuya Inagaki, Yosuke Yamamoto.

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