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The Added Value of Blood Glucose Monitoring in High-Risk Individuals Undergoing Pancreatic Cancer Surveillance

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Objectives: The study aimed to investigate the added value of blood glucose monitoring in high-risk individuals (HRIs) participating in pancreatic cancer surveillance.

Materials and Methods: High-risk individuals with a *CDKN2A/p16* germline pathogenic variant participating in pancreatic cancer surveillance were included in this study. Multivariable logistic regression was performed to assess the relationship between new-onset diabetes (NOD) and pancreatic ductal adenocarcinoma (PDAC). To quantify the diagnostic performance of NOD as a marker for PDAC, receiver operating characteristic curve with area under the curve was computed.

Results: In total, 220 HRIs were included between 2000 and 2019. Median age was 61 (interquartile range. 53–71) years and 62.7% of participants were female. During the study period, 26 (11.8%) HRIs developed NOD, of whom 5 (19.2%) later developed PDAC. The other 23 (82.1%) PDAC cases remained NOD-free. Multivariable analysis showed no statistically significant relationship between NOD and PDAC (odds ratio, 1.21; 95% confidence interval, 0.39–3.78) and 4 of 5 PDAC cases seemed to have NOD within 3 months before diagnosis. Furthermore, NOD did not differentiate between HRIs with and without PDAC (area under the curve, 0.54; 95% confidence interval, 0.46–0.61).

Conclusions: In this study, we found no added value for longitudinal glucose monitoring in *CDKN2A* pathogenic variant carriers participating in an imaging-based pancreatic cancer surveillance program.

Key Words: early detection, new-onset diabetes, pancreatic ductal adenocarcinoma, risk stratification

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BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is one of the top five leading causes of cancer death, accounting for 7–8% of all cancer deaths in the United States.[1,2] Moreover, there is a growing incidence of PDAC worldwide.[3–6] This trend is concerning because of the aggressive nature of this type of cancer and its low 5-year survival rate of 5–10%.[7,8] More than 80% of patients with PDAC are diagnosed at an advanced stage. This diagnostic delay contributes to the poor prognosis.[9,10] Therefore, it is essential to detect PDAC at an earlier stage in order to improve survival outcomes; however, this still remains a challenge.[11,12]

Despite the growing disease burden, population-based screening is impractical due to the relatively low disease incidence, which ultimately results in high rates of false-positives.[13] Additionally, unavailability of accurate diagnostic biomarkers and imaging techniques contributes to the lack of success in screening.[14,15] However, PDAC incidence within familial and hereditary PDAC groups is higher and is estimated to account for 10% of all cases, with lifetime risk ranging between 2.2–53.3% in specified high-risk groups.[16,17] Targeted surveillance by imaging in certain high-risk individuals (HRIs) has shown promising results in various studies and is therefore recommended by the international guidelines.[18–20] Nevertheless, most PDAC patients are still detected in a phase where cure is no longer an option; for this reason, there is an urgent need for novel, accurate biomarkers.[21,22]

There is growing evidence that new-onset diabetes (NOD) is associated with PDAC and that it could be used as a biomarker to identify individuals at a higher risk, consequently promoting the detection of PDAC at an earlier stage in the general population.[23–26] In fact, findings from Sah et al[27] suggest that NOD can be found up to 3 years prior to PDAC diagnosis. However, this needs further validation and still little is known about NOD among HRIs undergoing longitudinal surveillance. The NOD can be based on type 3c diabetes mellitus (T3cDM), which is diabetes secondary to pancreatic disease, or type 2 diabetes mellitus (T2DM). Both types of diabetes have distinct underlying mechanisms and so they also carry a different kind of risk for PDAC, of which T3cDM carries the greatest risk.[28] Thus far, it remains challenging to identify NOD based on T3cDM and distinguish it from T2DM, especially in this obesity pandemic.[29]

The International Cancer of the Pancreas Screening (CAPS) consortium guideline recommends including glucose measurement in routine monitoring; however, its effectiveness has not been proven yet in surveillance of HRIs next to longitudinal imaging, as acknowledged by the guideline.[30] Therefore, this study has been set up to investigate the added value of glucose as a biomarker for PDAC in a high-risk surveillance cohort undergoing longitudinal imaging.

MATERIALS AND METHODS

Study Design and Data Source

This is a retrospective analysis on prospectively collected data from a pancreatic cancer surveillance program conducted at the Department of Gastroenterology and Hepatology in Leiden University Medical Center. High-risk individuals with a *CDKN2A/p16* germline pathogenic variant (PV) participating in pancreatic cancer surveillance with at least one fasting blood glucose (FBG) and/or hemoglobin A1c (HbA1c) measurement were included in the study. For this study, time of enrollment was defined as the first blood glucose measurement. Individuals with diabetes at baseline, less than 3 years of follow-up, and all follow-up time after pancreatectomy were excluded from the study. High-risk individuals who developed NOD during the study were considered exposed. High-risk individuals who did not develop NOD served as the control group. The outcome of the study was PDAC diagnosis confirmed by histopathology or, when not available, based on imaging.

Data on HRIs was collected from the Leiden University Medical Center pancreatic cancer surveillance program that was set up in 2000. Surveillance consists of an annual magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), and since 2012 also an optional endoscopic ultrasound (EUS) every 12 months, alternating every 6 months with MRI. Thus, individuals who received both MRI and EUS imaging underwent surveillance every 6 months. When new concerning lesions were detected, the surveillance interval was shortened to 3–6 months or EUS-guided sampling was performed. Blood glucose measurements were taken annually at time of surveillance examination. A detailed description of the surveillance program is described in a previous study.[21]

Data Collection and Definitions

From January 2000 to May 2019, data was collected on demographics, comorbidities, lifestyle, glucose measurements, results of MRI and EUS examinations, and pathology reports. New-onset diabetes was defined using either FBG cutoff value of ≥ 7 mmol/L or HbA1c value of ≥48 mmol/mol. To confirm the diagnosis, patients required two consecutive, abnormal FBG values, or one abnormal HbA1c measurement. An exception to this were individuals with one abnormal FBG measurement, which happened to be the last measurement within 3 years of PDAC diagnosis. In that case, one abnormal FBG measurement was sufficient to label the subject with NOD.

Statistical Analyses

Data were presented as mean ± standard deviation (SD) or median ± interquartile range (IQR), based on their distribution. Univariable logistic regression was used to explore the relationship between NOD and PDAC. To correct for sex, age, body mass index (BMI), and smoking history as potential confounders, multivariable logistic regression was performed. For patients with missing BMI and smoking history data, missing data was assumed to be at random and multivariable imputation via chained equations was implemented. The number of needed imputed data sets was based on the quadratic rule, and all generated data sets were individually analyzed using multivariable logistic regression. After that, the results were pooled and exponentiated into odds ratios (ORs). In order to quantify the diagnostic performance of NOD as a marker for PDAC, receiver operating characteristic curve and area under the curve (AUC) were computed. P values were two-sided and findings were considered statistically significant when $P < 0.05$. All statistical analyses were carried out using R version 4.2.1.

RESULTS

Study Population

Of 378 HRIs with a confirmed *CDKN2A/p16* PV participating in the surveillance program, 220 were enrolled in the study, as shown in Figure 1. The vast majority of those excluded had a follow-up of less than 3 years (n = 112). Table 1 shows the baseline characteristics of all included HRIs. The median age was 61 (IQR 53–71) years, and 62.7% was female.

Patients With NOD Who Developed PDAC

In total, 26 HRIs developed NOD during the entire follow-up period, of whom, 5 (19.2%) later developed PDAC. The other 23 (82.1%) PDAC cases remained NOD-free. In two patients (*P2* and *P18*), NOD was found at time of PDAC diagnosis. In *P4* and *P9*, NOD was found 2 and 3 months before the PDAC diagnosis, respectively. In the last patient, NOD was found 1 year before PDAC diagnosis. A detailed overview of all HRIs who developed PDAC is shown in Table 2. Notably, one individual with NOD triggered an extra MRI scan, which was performed 6 months after a negative MRI scan. However, that individual did not develop PDAC in this study.

P9 is an example of a patient who developed PDAC after NOD. The longitudinal FBG measurements are shown in Figure 2. The initial FBG measurement of *P9* was 8.2 mmol/L. Subsequently, there was a decline in glucose levels, followed by an upward trend 5 years later to 7.1 mmol/L. Two years after this, another decline was observed, with concentration of FBG levels dropping to 4.7 mmol/L. This decrease in FBG levels was followed by an increase reaching 8.2 mmol/L; concomitantly, PDAC diagnosis was made. Longitudinal FBG trends for all patients who developed both NOD and PDAC, as well as PDAC cases who did not develop NOD, can be found in Supplemental Figures 1, http://links.lww.com/MPA/B133, and 2, http://links.lww.com/MPA/B134, respectively.

Relationship Between NOD and Pancreatic Ductal Adenocarcinoma

Multivariable logistic regression showed no statistically significant relation between NOD and PDAC (OR 1.21; 95% confidence interval [CI], 0.39–3.78; Table 3). A statistically significant association was, exclusively, found between age and PDAC (OR 1.05; 95% CI, 1.01–1.1). Individuals with a positive smoking history had a nonsignificant increased OR of 2.32 (95% CI, 0.94–5.77) of

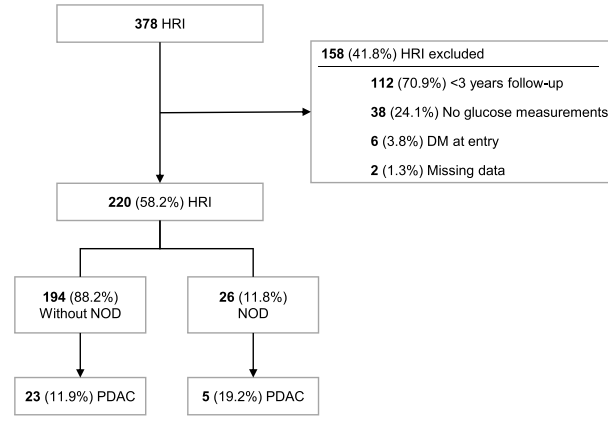

FIGURE 1. Flowchart of the study population. DM, diabetes mellitus.

TABLE 1. Characteristics of the Study Population, Subdivided Into Individuals Who Did Not Develop NOD (n = 194) and Individuals Who Developed NOD (n = 26) During the Study Period

	Total (N = 220)	Without NOD (n = 194)	NOD (n = 26)
Age, years, median (IQR)	61 (53.0–71.0)	59 (53.0–69.0)	68.5 (62.0–71.8)
Sex, n (%)			
Female	138 (62.7)	124 (63.9)	14 (53.8)
Male	82 (37.3)	70 (36.1)	12 (46.2)
BMI, mean ± SD			
Total	26.2 ± 4.1	26.4 ± 4.5	25.7 ± 2.5
BMI ≥ 25, n (%)	118 (53.6)	105 (54.1)	13 (50.0)
Smoking, n (%)			
Current	20 (9.1)	19 (9.8)	1 (3.8)
Pack years, median (IQR)	24.0 (20.0)	15.2 (5.0–23.8)	30.0 (0)
Missing (%)	1 (5.0)	1 (5.3)	-
Former	99 (45.0)	81 (41.8)	18 (69.2)
Pack years, median (IQR)	11 (24.0)	10 (4.0–20.0)	20 (7.5–30.0)
Missing (%)	6 (6.1)	4 (4.9)	2 (11.1)
Never	99 (45.0)	92 (47.4)	7 (26.9)
Missing (%)	2 (0.9)	2 (1.0)	-
Alcohol units per week, n (%)			
Abstinent	46 (20.9)	43 (22.2)	3 (11.5)
0–7 (light)	79 (35.9)	68 (35.1)	11 (42.3)
7–21 (moderate)	62 (28.2)	57 (29.4)	5 (19.2)
21–42 (heavy)	15 (6.8)	11 (5.7)	4 (15.4)
Missing (%)	18 (8.2)	15 (7.7)	3 (11.5)
CDKN2A variant, n (%)			
p16-Leiden PV (Ala76Cysfs*64)	218 (99.1)	192 (99.0)	26 (100.0)
Likely PV (Gly23Arg)	2 (0.9)	2 (1.0)	-
Glucose measurements, n (%)			
Serum only	117 (53.2)	102 (52.6)	15 (57.7)
Serum and HbA1c	103 (46.8)	92 (47.4)	11 (42.3)
No. measurements per individual, median (IQR)			
Serum	7 (4.0–10.0)	6 (4.0–9.8)	11 (8.0–19.0)
HbA1c	8 (6.0–13.0)	7.5 (6.0–11.2)	14 (12.0–21.5)

developing PDAC compared to nonsmokers. Furthermore, no difference was found in developing PDAC between sex and BMI.

The Diagnostic Performance of NOD as a Marker for Pancreatic Ductal Adenocarcinoma

Area under the receiver operating curve curve is presented in Figure 3. The estimated AUC is equal to 0.535 (95% CI, 0.459–0.610), which is not significantly different from perfect random chance. Therefore, NOD does not discriminate between HRIs with and without PDAC.

DISCUSSION

This is the first longitudinal study assessing the relationship of NOD and PDAC in surveillance of HRIs. In this follow-up study of carriers with a germline *CDKN2A/p16* PV, we found no added value of glucose measurements in surveillance next to longitudinal imaging. Although almost 20% of HRIs with NOD have developed PDAC, elevated glucose values were still insufficient to discriminate between HRIs with and without PDAC. This data suggests that NOD, as a biomarker in its current form, should not be used as a tool to stratify our surveillance population.

Little is known about NOD and PDAC among surveillance of HRIs. One study by Shah et al.[31] described an occurrence of NOD in one patient with PDAC. However, this provides insufficient evidence to support an association. Moreover, in their study, only one FBG measurement was obtained in each individual, therefore the diagnosis of NOD was not confirmed. Furthermore, because the study design was cross-sectional, the interval between NOD and PDAC could not be determined. To our knowledge, this was the only study previously conducted on NOD and PDAC among HRIs. In this cohort, 19.2% of individuals with NOD developed PDAC within 3 years. A retrospective study consisting of 2122 NOD individuals from the general population found that only 0.85% of these individuals developed PDAC within 3 years.[32] While our cohort shows a significant higher prevalence of PDAC among NOD individuals, it is important to take into consideration that the prevalence of PDAC among individuals without NOD in our cohort is also considerably high (11.9%). Based on our study with longitudinal glucose measurements showing no association between elevated glucose levels and PDAC diagnosis, there is currently lack of evidence supporting the added value of glucose measurements in HRIs. We feel that glucose measurements should not be recommended in routine monitoring of HRIs already undergoing annual surveillance.

Considerably more studies have been done in the general population, which indicate an association between NOD and PDAC.[32–36] These studies suggest that NOD could be used to identify a

TABLE 2. Details of HRIs Who Developed PDAC During the Follow-up of the Study (n = 28)

No.	Diagnosis Year	Age at Diagnosis, Years/Sex	Follow-up Duration, Months	Detection Modality	Time Since Previous Examination, Months	TNM Stage	Interval From NOD to PDAC, Months	FBG Level Prior to NOD Diagnosis, Mmol/L	FBG Level at NOD Diagnosis, mmol/L	Time Between FBG Measurements Prior to and at NOD Diagnosis, Months	No. Glucose Measurements
P1	2006	57/M	39	MRI/MRCP	12	pT4N2M0	-	-	-	-	2
P2	2008	57/F	34	MRI/MRCP	28	pT2N0M0	0	4.6	8.1	33.5	2
P3	2008	62/F	3	MRI/MRCP	-	pT3N0M0	-	-	-	-	1
P4	2009	48/M	3	MRI/MRCP	-	pT3N0M0	2	-	7.6	-	1
P5	2010	47/F	4	MRI/MRCP	-	pT3N2M0	-	-	-	-	1
P6	2011	63/F	91	MRI/MRCP	11	cT2N2M0	-	-	-		8
P7	2012	39/M	17	MRI/MRCP	-	pT2N2M0	-	-	-	-	1
P8	2012	55/F	131	MRI/MRCP	12	pT3N0M0	-	-	-	-	6
P9	2014	66/F	143	CT	22	cT4N0M0	3	4.7	8.2	18.6	10
P10	2014	58/M	91	CT	10	cT4N0M0	-	-	-	-	7
P11	2014	74/F	83	MRI/MRCP	12	pT1cN0M0	-	-	-	-	6
P12	2015	50/M	44	MRI/MRCP	9	pT3N0M0	-	-	-	-	1
P13	2016	64/F	2	MRI/MRCP	-	cT2N0M0	-	-	-	-	1
P14	2016	51/F	86	Abdominal Ultrasound	5	pT3N0M0	-	-	-	-	8
P15	2016	67/F	119	MRI/MRCP	11	pT3N1M0	-	-	-	-	10
P16	2016	62/M	68	MRI/MRCP	12	pT1cN1M0	12	4.8	8.1	12.2	3
P17	2016	61/F	161	MRI/MRCP	12	pT1aN0M0	-	-	-	-	8
P18	2017	65/M	172	CT	8	pT3N0M0	0	5.2	7.5	7.8	11
P19	2017	63/M	7	MRI/MRCP	3	pT1bN0M0	-	-	-	-	1
P20	2017	71/M	71	MRI/MRCP	13	pT3N0M0	-	-	-	-	6
P21	2018	49/F	3	MRI/MRCP	-	cT4N0M1	-	-	-	-	1
P22	2018	69/F	211	MRI/MRCP	13	pT2N2M0	-	-	-	-	34
P23	2018	63/F	127	MRI/MRCP	12	pT2N0M0	-	-	-	-	5
P24	2018	59/F	7	MRI/MRCP	-	cT4N0M0	-	-	-	-	1
P25	2019	48/F	121	MRI/MRCP	16	cT2N0M0	-	-	-	-	14
P26	2019	60/F	3	MRI/MRCP	-	cT1cN0M0	-	-	-	-	1
P27	2020	61/M	125	CT	4	cT4N1M1	-	-	-	-	11
P28	2020	50/F	88	MRI/MRCP	8	cT1bN0M0	-	-	-	-	8

CT indicates computed tomography; F, female; FBG, fasting blood glucose; M, male; P, patient.

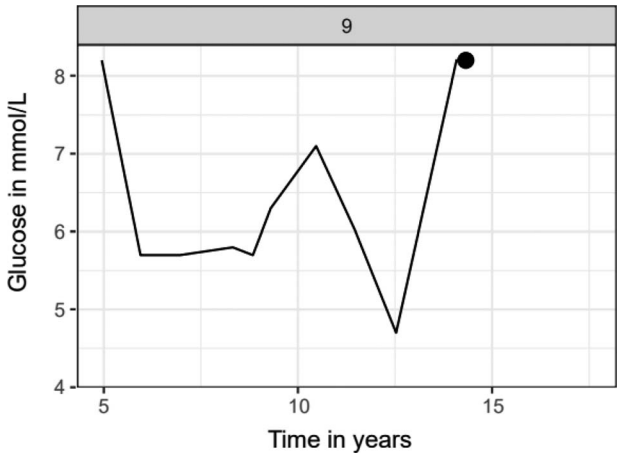

FIGURE 2. Longitudinal fasting blood glucose levels for patient 9 (P9) undergoing surveillance for pancreatic cancer who was diagnosed with pancreatic ductal adenocarcinoma after NOD during the follow-up of the study.

population at increased risk of PDAC and that these individuals should potentially be offered surveillance.[32–36] However, studies using predictive modeling in individuals with NOD among the general population show that NOD should not be used as a solitary criterion to recommend PDAC surveillance.[23,37,38] On top of this, small changes in glucose levels could already signify an increased PDAC risk, but these changes are often so subtle that they are difficult to pick up in routine care, certainly with NOD as a biomarker.[39] As shown in the previous studies, a panel of several biomarkers including demographic, lifestyle and clinical variables might provide more accuracy and could resolve this issue. Upcoming prospective studies among the general population have been set up to provide more insight into the relationship between NOD and PDAC within a few years.[40,41]

The relationship between PDAC and DM is fairly complex due to the bidirectional link between the two. Type 2 diabetes mellitus is

TABLE 3. Results From Univariable and Multivariable Logistic Regression Assessing the Relation Between NOD and PDAC

	Univariable Model			Multivariable Model		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
NOD						
No		1.00			1.00	
Yes	1.77	0.60–5.18	0.30	1.21	0.39–3.78	0.74
Age, years	1.05	1.01–1.09	0.02	1.05	1.01–1.10	0.02
BMI						
18.5 ≥ − < 25		1.00			1.00	
≥25	0.77	0.33–1.76	0.53	0.76	0.32–1.80	0.53
Sex						
Male		1.00			1.00	
Female	1.08	0.47–2.48	0.86	1.25	0.52–3.00	0.62
Smoking history*						
No		1.00			1.00	
Yes	2.31	0.97–5.53	0.06	2.32	0.94–5.77	0.07

*Positive smoking history defined as an individual being a current or former smoker.

P indicates probability value.

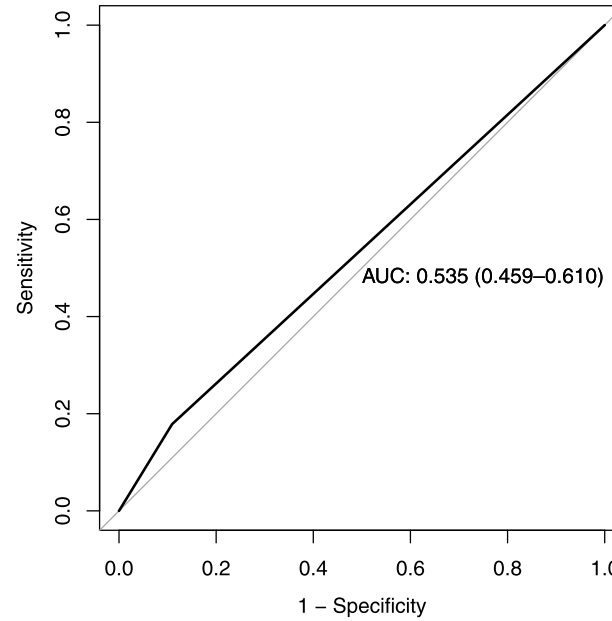

FIGURE 3. Receiver operating curve of NOD in high-risk individuals for pancreatic ductal adenocarcinoma showing the AUC with 95% confidence interval.

an established risk factor for PDAC. Its underlying mechanism is explained by high-insulin levels, which can activate insulin-like growth factor and, in its turn, promote mitogenic effects.[42–44] On the other hand, there is also evidence of PDAC being the cause of diabetes (T3cDM).[27] The risk for PDAC in T2DM and T3cDM is different due to the distinct underlying mechanisms. Despite this, the two conditions are difficult to distinguish. The high incidence of T2DM, especially in the age group above 45 years, makes the distinction between the two even more challenging.[45–47] Sharma et al.[23] solved this problem by taking both blood glucose values and weight loss into consideration. T3cDM is more often associated with weight loss, while T2DM is typically characterized by weight gain.[48] This was confirmed by a recent meta-analysis.[28] A different strategy to distinguish the two forms of diabetes could be the use of other biomarkers. Several studies have been done on biomarkers like adiponectin, microRNAs, and different metabolites to discern between these two types of diabetes; however, there is not yet a standardized method to do so.[49–51] Therefore, more research needs to be done on potential biomarkers in order to differentiate between NOD based on T2DM and T3cDM.

The time frame of the included glucose measurements should also be taken into consideration. We examined all glucose measurements only up to, and including the date of PDAC diagnosis. Pancreatic ductal adenocarcinoma diagnoses were made based on histopathology, and when this was not available, imaging was used. The advantage of glucose is that it is relatively noninvasive and can be measured at various times throughout the year. However, the structural changes in the pancreas that induce T3cDM often occur at a later stage and NOD may therefore have no added value in the detection of small tumors in addition to imaging.[52] High-resolution imaging may be more likely to detect the tumors before alterations in blood glucose levels occur, which could explain the lack of association between NOD and PDAC in this study. This observation is in conjunction with the research conducted by Sharma et al.,[52] where hyperglycemic signals were found to be most prominent in large tumors and diminish as tumor volume decreases. It could be argued that measuring more often could result in an earlier identification of NOD

and therefore an earlier PDAC diagnosis; however, this does not have to be true. Glucose levels vary over time, so measuring more often could lead to an incomprehensible picture, as shown in Figure 2, in which the significance of high and low glucose levels are difficult to interpret. Consequently, patients could end up in intensified surveillance, which could impose extra strain on the patients. In addition to this, to obtain glucose measurements, patients have to travel on an empty stomach to the nearest hospital. This time and energy investment should be proportionate to the benefits. Additionally, the lead time does not seem that impressive in this study (Table 2). In fact, four out of five PDAC cases appeared to have developed NOD 3 months prior to diagnosis. It is worth noting that glycemic assessments were done on an annual basis, and that increasing the frequency could potentially result in an earlier NOD diagnosis. While our study shows no added value of glycemic evaluation in individuals undergoing surveillance next to longitudinal imaging, a future study may assess the benefit of biannual glycemic evaluation in order to establish a comprehensive understanding of its effectiveness. Additionally, we endorse the exploration of alternative strategies using glycemic parameters, including the consideration of lowering glucose thresholds or incorporating scoring methods, such as the enriching new-onset diabetes for pancreatic cancer score.[23] Moreover, a future study should be conducted to evaluate the added value of HbA1c in pancreas surveillance. However, it is important to note that HbA1c represents a 3-month average and will not be able to capture acute blood glucose dysregulations.

The first limitation of this study is the small number of cases, which is due to the relatively few individuals undergoing surveillance. This sequentially reduces power and results in rough effect estimates with wider confidence intervals. In the future, this issue could be resolved by conducting the study within an international multicenter setting, thereby increasing the sample size. A second limitation is the homogeneity of the study population of individuals with a *CDKN2A/p16* PV. The study by Pal et al.[53] shows that a loss of function of *CDKN2A* is associated with increased beta cell activity and a disruption of insulin sensitivity. The involvement of this tumor suppressor gene in glucose homeostasis makes the results less generalizable to other HRI cohorts. Therefore, it is crucial to highlight that our findings may not necessarily apply universally to other surveillance cohorts, and we encourage the replication of this study for broader validation. Third, it cannot be guaranteed with certainty that all blood glucose tests were sampled preprandial. This reflects the use of FBG in daily medical practice and the potential problems that can arise during sampling. The fourth limitation is that abnormal FBG levels were not confirmed by repeating the measurements on different days, thereby decreasing the accuracy. The fifth limitation of this study is the small number of HbA1c measurements that were collected. As a result, little can be deducted about HbA1c use among HRIs undergoing surveillance.

This is the first study evaluating the association between NOD and PDAC diagnosis using longitudinal glucose measurements in a HRI surveillance program. Our study shows that NOD on its own has no added value in surveillance of *CDKN2A* PV carriers next to longitudinal imaging; therefore, it should not be used as a mean to stratify the PDAC surveillance cohort yet. In the future, NOD could potentially play a role in risk stratification, however more research needs to be done in order to distinguish NOD based on T3cDM and different panels of biomarkers should be explored to accurately diagnose PDAC at an early stage.

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