University of Szeged

Albert Szent-Györgyi Medical School

Doctoral School of Theoretical Medicine

Early detection of pancreatic ductal adenocarcinoma – new opportunities of screening

PhD Thesis

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1. List of publications

1.1 Related to this thesis

1. **Illés D, Terzin V, Holzinger G et al. New-onset type 2 diabetes mellitus – a high-risk group suitable for the screening of pancreatic cancer? *Pancreatology*. 2016;16(2):266-71. IF: 2.58 SJR indicator: Q2.**

2. Illés D, Torday L, Czakó L. A pancreascarcinoma korszerű kezelése. *Onkológia & hematológia*. 2016;5:22-30.

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4. Illés D, Czakó L. A hasnyálmirigyrák Világnapja 11.21. – Lankadatlan éberség! *Lege Artis Medicinae*. 2019;29(12):643-646. SJR indicator: Q4.

5. Illés D, Czakó L. A diabetes és az emésztőrendszer betegségei: pancreatitis és emésztőrendszeri tumorok. *Magyar Belorvosi Archívum*. 2020;73:63–67.

6. **Illés D, Iványi E, Holzinger G et al. New Onset of DiabetEs in aSsociation with pancreatic cancer (NODES trial): Protocol of a Prospective, Multicentre Observational trial. *BMJ Open*. 2020;10(11):037267. IF: 2.692 SJR indicator: Q1.**

1.2 Not related to this thesis

1. Illés D, Urbán E, Lázár A et al. Az antibiotikumrezisztencia változása cholangitisben: klinikai tapasztalataink. *Orvosi Hetilap.* 2019;160(36):1437-1442.
2. Illés D, Czakó L. Rate of early hospital readmission in acute pancreatitis as a quality marker. *Orvosi Hetilap*. 2021;162(11):413-418.
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1.2.1 Co-Author as a member of the Hungarian Pancreatic Study Group

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Scientometrics

Number of full publications	29
First author publications	8
Hirsch index	10
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2. Introduction

2.1. Importance of the topic

Among the malignant diseases of the pancreas, the pancreatic ductal adenocarcinoma (PDAC) is the most common one: it accounts for more than 90% of the malignant tumours of the exocrine pancreas. Although it is a rare disease with a lifetime prevalence of 1.39%, PDAC is a very aggressive disease with a poor prognosis: it evolves asymptomatically or with aspecific symptoms for a long time so the patients will be diagnosed in a late, advanced stage, when the only curative therapy, the surgical resection is already impossible because of the presence of metastases and locoregional infiltration. Therefore the mortality/morbidity rate of PDAC is ~1. The incidence of PDAC is rising at a rate of 0.5% to 1% per year therefore PDAC is projected to become the second-leading cause of cancer death by 2030. Complications of advanced PDAC are extremely stressful for patients and involve significant hospital costs. All of this could be avoided if the disease were detected at an early stage when it is still operable. Unfortunately, there is no effective screening program yet.

Given that PDAC is a rare disease with low lifetime-prevalence a population-wide screening would be ineffective and a huge financial burden on the healthcare system. Therefore it is recommended that patients who are at high risk of PDAC should be screened. Among risk factors diabetes mellitus (DM) has the strongest link to PDAC: 40-65% of patients diagnosed with PDAC meet the criteria for DM.

DM counts as a worldwide epidemic with increasing incidence in recent decades: it is predicted that the number of people with DM will increase to 300 million by 2025 and 366 million by 2030. This represents a huge number of new patients each year, so screening this large group for PDAC would not yet be cost-effective; further narrowing of the target group is needed by investigating the association between PDAC and DM.

2.2. Bidirectional connection/ dual causality with diabetes mellitus

The association between PDAC and DM has been known for decades. In epidemiological studies the increased incidence of gastrointestinal malignancies has been repeatedly observed in population with diabetes. The relative risk ranges from 1.3-4.7.

Interestingly, patients with short-term DM (<4 years) have more than 1.5-fold risk of displaying PDAC as compared with patients who are diabetic for more than 5 years. Pannala et al. reported that the patients diagnosed with type-2 diabetes mellitus (T2DM) have an 8-fold risk of

developing PDAC within 2-3 years from the diagnosis of T2DM relative to the general population.

Based on the above, the connection between PDAC and DM is bidirectional: the „long term" DM is a risk factor, the „short term" DM is a presumably paraneoplastic consequence of the PDAC. The „short term" DM was called „new-onset" DM in the literature. The precise definition for this entity is DM diagnosed within 36 months. *Patients with new-onset DM may be an appropriate group for pancreatic cancer screening, which should be statistically supported.*

Older age would further enrich the group eligible for screening for PDAC, as age is an independent risk factor for PDAC - in newly diagnosed diabetic patients over 50 years of age, the incidence of PDAC is approximately 1%.

2.3 Pancreatogenic diabetes

For decades PDAC-related DM was presented in the literature as one of the manifestations of pancreatogenic diabetes (T3cDM), it accounts for only 9% of T3cDM cases. PDAC-related DM is a paraneoplastic phenomenon associated with the tumour of the pancreas. One hypothesis about the pathomechanism is that the development of diabetes is a result of substances secreted by the tumour. In a study of 104 patients underwent resection because of pancreatic cancer, of whom 41 had DM at the time of surgery, it was found that 57% of the patients with new-onset DM had resolution of their DM postoperatively, whereas 100% of the patients with long-standing DM remained diabetic after pancreatic resection.

Based on the above, neither pancreatic exocrine insufficiency (PEI) nor pathological pancreatic imaging as diagnostic criteria for T3cDM are necessarily present in PDAC-related DM. Therefore, the diagnostic criteria for T3cDM alone would not be effective in screening for PDAC-related DM, as these tests are difficult to obtain, expensive, burdensome for patients and therefore not suitable for screening.

2.4 Diabetes of the exocrine pancreas

The controversy that PDAC-related DM as a form of T3cDM does not necessarily shows the signs of PEI or pathological imaging highlighted the need to rethink the nomenclature of pancreatogenic DM. Among others, diabetes in diseases of the exocrine pancreas (DEP) contains the special entity new-onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma (NOD-PDAC).

Considering that the new nomenclature for DEP started to be used in 2021, in our own research, the group of NOD-PDAC patients is referred to as PDAC-T3cDM. *Among newly diagnosed diabetic patients differentiating "simple" T2DM from NOD-PDAC is important, but requires a new diagnostic approach.*

2.5 Current diagnostic opportunities for screening

Among blood tests, measuring the serum level of tumourmarkers as possible screening modalities is promising, as these are cheap, easy to perform and widely available. Currently the carbohydrate antigen 19-9 (CA 19-9) is the only blood based biomarker in clinical use for PDAC.

CA 19-9 is a tumour-associated, but not tumour-specific epitope of sialyated Lewis A blood group antigen. The sensitivity of this marker for PDAC is 70-90%, the specificity is 90%, the positive predictive value is 69% and the negative predictive value is 90% so it is *recommended to combine CA 19-9 measurement with an other technique for screening*.

Imaging is the gold standard for diagnosing PDAC. The first choice is transabdominal ultrasonography (US), but its sensitivity in diagnosing PDAC is only 50-70%. Its accuracy is low for tumours <1 cm, which are usually operable, and is negatively affected by obesity and meteorism. Computer tomography (CT), endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography also have a high likelihood of correct diagnosis, but the low prevalence of PDAC combined with the patient burden of radiation exposure and endoscopic procedures and with the high costs of these interventions precludes their use in screening. *However, US is easy to use, widely available, non - invasive and relatively inexpensive, making it an ideal screening modality.*

As mentioned above, a blood test would be an ideal screening method. Metabolomics, including lipidomics, has recently become more feasible, allowing the identification of clinical metabolite biomarkers. A biomarker panel consisting of nine metabolites plus the established protein CA 19-9 was recently identified by Mayerle et al. with 89.9% sensitivity, 91.3% specificity and 99.8% negative predictive value (NPV) for differentiating PDAC from chronic pancreatitis.

Using the same methods, a biomarker panel was identified for the differential diagnosis of NOD-PDAC and non - cancer related diabetes. *Provided the biomarker is validated, the panel could be effective in screening for NOD-PDAC in the high-risk group of elderly patients with new-onset DM.*

3. Aims

3.1 Study A - New-onset type 2 diabetes mellitus – a high-risk group suitable for the screening of pancreatic cancer? (HiRiPaC study)

In our first study, we aimed to provide statistical support that patients with new-onset DM may be an appropriate group for pancreatic cancer screening. We set out to determine the incidence of PDAC prospectively in new-onset T2DM patients. The screening method included the measurement of serum CA 19-9 levels combined with the performance of abdominal ultrasound (US).

3.2 Study B – New-Onset of DiabetEs in aSsociation with pancreatic ductal adenocarcinoma (NODES trial)

In our second study, we aim to differentiate 'simple' T2DM from NOD-PDAC in newly diagnosed diabetic patients by validating a biomarker panel as a screening method in the high-risk group of elderly patients with new-onset DM. We aim to diagnose PDAC in an early operable stage and to estimate the incidence of PDAC in patients with new-onset diabetes.

4. Patients and methods

4.1 Study A – HiRiPaC Study

4.1.1 Patients

Between March 2012 and October 2014, 115 consecutive patients with new-onset T2DM were enrolled in this prospective study by diabetologists at our clinic. The diagnosis of T2DM was made according to the American Diabetes Association (ADA) criteria. Cases with T1DM and any type of symptoms suggestive of pancreatic disease were excluded. The duration of follow-up was 36 months from the first visit. All patients gave written informed consent to participate in the study. The study protocol was in full compliance with the latest tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Szeged (approval number 97/2012).

4.1.2 Methods

Serum CA 19-9 levels were measured and transabdominal US was performed at the first visit. In accordance with local laboratory standards, the cut-off serum CA 19-9 level was 27 U/mL. If the transabdominal US showed an abnormality (with either a normal or elevated CA 19-9 level), abdominal computed tomography (CT) was performed. Endoscopic ultrasound (EUS), EUS-guided fine needle aspiration (EUS-FNA) and surgical referral were performed if CT

showed a pancreatic lesion. Abdominal CT was performed in the presence of an elevated serum CA 19-9 level without US abnormality. If the CT showed no lesion, the serum CA 19-9 level was repeated after 3 months. If the CA 19-9 level was normal and the US was negative, the CA 19-9 level was measured every 6 months and the US was performed every year.

To assess the suitability of patients with new-onset T2DM as a risk group for PDAC, the standardized incidence ratio (SIR) was calculated using the person-time incidence based on our study and the age-adjusted incidence of PDAC in Hungary (9.3 cases/100.000 persons). A SIR of 1 indicates that the number of cancer cases observed in the assessed population is equal to the number of cancer cases expected in the general population. An SIR > 1 indicates that there were more cancer cases than expected. To assess the effectiveness of CA 19-9 and US as potential diagnostic tools for PDAC, sensitivity, specificity, positive and negative predictive values were calculated.

4.2 Study B – NODES trial

4.2.1 Patients

4.2.1.1 Design

NODES is a prospective, multicenter, observational cohort study aiming to validate a biomarker panel in the early stage of PDAC. We included patients over 60 years of age diagnosed with diabetes within 6 months (newly diagnosed) - diagnostical criteria are based on the Diabetes Control and Complications Trial – who signed the written informed consent. (1) Continuous alcohol abuse (2) chronic pancreatitis (3) previous pancreas operation/pancreatectomy (4) pregnancy (5) present malignant disease and type 1 DM count as exclusion criteria. Patients with chronic pancreatitis were excluded because a metabolic signature that differentiates between chronic pancreatitis and patients with PDAC has already been published and is being further evaluated by the META-PAC consortium, while the present study aims to differentiate between patients with NOD-PDAC and new-onset diabetes due to other causes.

4.2.1.2 Sample size

Considering the epidemiological data suggesting that the prevalence of PDAC in Hungary is significantly higher than in other countries, we assumed a prevalence of 2% for PDAC. Based on these data, the sample size calculation suggests that 2661 patients would need to be enrolled to confirm or reject the hypothesis for the primary endpoint with a 10% drop-out rate, 80% power and 95% significance level.

4.2.1.3 Duration

The first recruitment centre was initialized on 1 July 2019. Start of patient recruitment: 31 January 2020. All enrolled patients will be followed for 36 months. *Due to the COVID 19 pandemic, the study is still ongoing. The delay of almost three years was caused by the reduced capacity of the health system as it tried to cope with the pandemic and is the consequence of central restrictions on outpatient care.*

4.2.1.4 Clinical data and clinical end points

Age, sex, body weight, body mass index, date of DM diagnosis, date of sampling, comorbidities, antidiabetic medication, clinical symptoms, histology and stage of PDAC were recorded. Data collection by questionnaire and blood samples were taken from all patients. Data were stored in a personalized electronic database (electronic case report form - eCRF).

Primary clinical end points are the sensitivity, specificity, PPV, NPV and accuracy of the biomarker test. Secondary end points are (1) mortality rate of PDAC in patients with new-onset diabetes (2) the proportion of localized and resectable PDAC (3) change in body weight before visit 1 and during visits 2–6 (4) change in fasting blood glucose and hemoglobin A1c (HbA1c) before visit 1 and during visits 2–6 (5) antidiabetic medications and the risk of PDAC (6) presence of concomitant diseases (7) smoking and alcohol intake (8) incidence of PDAC in patients with new-onset diabetes (9) cost-benefit analysis.

The trial was registered on ClinicalTrials. gov (NCT04164602). The study has been approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (41085-6/2019). Protocol version: V1.0 08.01.2019.

4.2.2. Methods

4.2.2.1 Study protocol

Patients with DM were recruited by our diabetologist and collaborating general practitioners on the basis of a recent (<6 months) laboratory test. Visit 0 was scheduled within 2 weeks of referral. Patients who met the study entry criteria and who were not excluded were informed and offered to participate in the study, but a signed informed consent was required for inclusion.

Clinical data, body weight and worrisome features (unintentional weight loss: 5% of body weight within 6 months without knowing the reason, abdominal pain/discomfort, abnormal laboratory data, unstable glucose metabolism despite adequate diet and medical treatment and without intercurrent infection) were recorded at Visit 0, and a fasting blood sample was taken

for assessment of laboratory data and metabolomics. C-peptide and glutamic acid decarboxylase antibodies (GADA) were measured to classify diabetes at visit 0. Patients with type 1 DM were excluded. If worrisome features were present at Visit 0, magnetic resonance imaging (MRI) or EUS were performed. Unambiguous PDAC lesions (>1 cm or also seen on MRI) were referred to surgery for resection. Ambiguous lesions in the pancreas underwent EUS fine needle aspiration. PDAC was diagnosed by histological examination. Visits 1-5 were scheduled every 6 months. Clinical symptoms, body weight, laboratory data (fasting blood glucose, HbA1c, liver and kidney function, lipids, blood count) were collected at each visit. Blood for biobank and CA19-9 were collected every 12 months. Follow-up was completed after 36 months.

4.2.2.2 Biochemical methods

After informed consent, blood samples were collected from patients after fasting (overnight, at least 8 hours) in an EDTA tube. The blood tubes were centrifuged for 10 minutes within 2 hours of blood collection. The centrifuge was temperature controlled at 19°C-21°C. After centrifugation, the supernatant was carefully removed, transferred to a fresh 9 mL tube and gently mixed to homogenize any gradient that may have formed in the plasma supernatant. The plasma was then transferred in 0.5 mL aliquots to tubes and stored at -80°C in a dedicated freezer (≤6 hours from centrifuge to freezer). Biomarkers were determined by comparing metabolite levels in plasma samples from patients diagnosed with PDAC and cancer-free patients with diabetes. CA19-9 was measured centrally in a certified clinical laboratory using a cut-off of 37 U/mL as a classifier. The cost of the biomarker test, quality-adjusted life-years and incremental cost-effectiveness ratio are planned to be determined.

4.2.2.3 Metabolite profiling

GC - MS (gas chromatography) and LC-MS/MS (liquid chromatography - MS/MS) were used for a metabolite profiling approach. Proteins were removed from plasma samples (60 µl) by precipitation. Polar and non - polar fractions were then separated by the addition of water and a mixture of ethanol and dichloromethane for both GC - MS and LC - MS/MS analyses. For GC - MS analysis, the non - polar fraction was treated with methanol under acidic conditions to yield the fatty acid methyl esters derived from free fatty acids and hydrolyzed complex lipids. The polar and non - polar fractions were further derivatized with O – methyl - hydroxylamine hydrochloride to convert oxo groups to O - methyloximes and then with a silylating agent (N – methyl – N - (trimethylsilyl)trifluoroacetamide) prior to GC - MS analysis.

For LC-MS/MS analysis, both fractions were dried and then reconstituted in appropriate solvent mixtures. HPLC was performed by gradient elution with methanol/water/formic acid on reversed phase columns.

MxP lipids cover profiling of sphingolipids (ceramides, sphingomyelins and sphingobases). Total lipids were extracted from plasma by liquid/liquid extraction using chloroform/methanol. The lipid extracts were subsequently fractionated by normal phase liquid LC into different lipid groups according to the references. The fractions were analyzed by LC-MS/MS using electrospray ionization and atmospheric pressure chemical ionization with detection of specific multiple reaction monitoring transitions for sphingomyelins and ceramides, respectively.

4.2.2.4 Statistical methods

After data normalization descriptive statistics - mean, median, SD, quartiles and relative frequency - relative risk (dichotomous variables), independent two-sample t-test (continuous variable) in case of normal distribution, and Mann-Whitney U test in case of non-normal distribution are planned to be performed. Logistic regression are used to explore predictive factors. Associated statistical analyses are performed with a 0.05 error probability (type I error probability). Confidence intervals (CI) for sensitivity, specificity and accuracy are obtained for the cut-off prespecified in the training data using the Clopper and Pearson method for the binomial distribution. For PPV and NPV, CIs are obtained using the method of Gart and Nam for ratios of binomial parameters as implemented in the R package pairwise CI. When comparing the biomarker and CA19-9 on the test data, differences in sensitivity and specificity are planned to test using McNemar's test.

5. Results

5.1 Study A HiRiPaC Study

A total of 115 patients with new-onset T2DM were included in the study (49 male, 66 female, mean age: 58 ± 11 years, range: 32-85 years). 7 patients were subsequently excluded for various reasons: 1 man had T1DM, 1 woman had polycystic ovary syndrome, and 5 patients later declined to participate. The mean time between diagnosis of T2DM and inclusion in the study was 3.5 ± 4.4 months (range: 0-20 months).

Serum CA 19-9 levels were elevated in 10 patients (9%) (mean: 52.613 ± 23.13 U/mL), but none of them had morphological abnormalities on US or CT.

Imaging studies revealed a pancreatic mass in three patients. Of them, two had no elevated serum CA 19-9 level. The overall incidence of PDAC in our study was 2.78% (3/108). To calculate SIR the person-time incidence in our study was needed. The follow-up period of all participants was expressed in years and then summed up (162,42 years). The person-time incidence was (3/162,42*100) 1.847 cases/100personyear. The age-adjusted incidence in Hungary was 9.3/100.000 = 0.0093/100personyear. The value of SIR was 1.847/0.0093=198.6 (95% CI = 6.25 - 46.9).

The US examination clearly showed the pancreatic mass in two of the three patients. In the remaining one hundred and five negative cases, the possibility of false-negative findings was excluded by follow-up. CT was performed in eighteen patients (i.e. two patients with a positive US finding, ten with an elevated CA 19-9 level, four with incomplete US examinations and two with symptoms not suggestive of pancreatic disease). CT revealed a pancreatic mass in all three PDAC cases.

5.2 Study B – NODES trial

As the NODES trial is still ongoing due to delays caused by the COVID 19 pandemic, no final results are available at the time of writing. Blood samples from 58 patients with new-onset DM are currently being analyzed in Germany. Of these, 4 patients (6.8%) had PDAC diagnosed within 6 months of DM diagnosis.

6. Discussion

In our prospective study, we demonstrated that the incidence of PDAC in patients with new-onset diabetes mellitus was 198.6-fold higher than in the normal population. This is significantly higher than the previously reported 8-fold risk. In this retrospective study, Pannala et al. included patients diagnosed with PDAC and matched non-cancer patients. The presence of diabetes was not an inclusion criterion but a parameter studied. They included 512 patients with PDAC, of whom 41.6% were diabetic. Of these patients, 75% had new-onset diabetes. This means that this study did not distinguish between NOD-PDAC and T2DM cases. As a result, the cumulative risk of PDAC in this mixed DM group is lower than it would be in the NOD-PDAC group alone. In contrast, we included 108 new-onset diabetics in our study. During follow-up, we were only able to diagnose the NOD-PDAC patients because of the different study protocol. The limited number of cases could also cause some bias regarding the high value of the SIR.

New-onset T2DM can therefore be classified as a high-risk group for PDAC. Damiano et al. reported a similar incidence (5.2%) of PDAC in patients hospitalized for newly diagnosed DM (less than 30 days), because the instability of the DM required insulin treatment.

Our study has provided evidence that screening is beneficial for the detection of PDAC in asymptomatic patients with new-onset DM. However, our results were also discouraging because all 3 PDAC cases diagnosed in our screening program were at an advanced, unresectable stage. A previous retrospective study showed that the mean interval between the onset of DM and the diagnosis of PDAC was 10 months (range 5 - 29 months) (15). The mean time between diagnosis of DM and enrolment of patients in our study was 3.5 ± 4.4 months in the whole screened population and 3.7 ± 4 months in patients finally diagnosed with PDAC. Therefore, the fact that advanced cases were diagnosed in our study cannot be explained by a longer interval between the onset of DM and inclusion in the study.

In contrast to previous data, we have confirmed that neither determining serum CA 19-9 levels nor performing transabdominal US are effective screening methods for detecting PDAC at an early stage. Both the sensitivity and positive predictive value of CA 19-9 were zero, and the false positive rate was 9% in our study. The mean value of elevated CA 19-9 levels in our study was only 52.613 ± 23.13 U/mL. However, the optimal cut-off value of CA 19-9 to differentiate between benign and malignant pancreatobiliary disease has been shown to be 70.5 U/mL (82.1% sensitivity, 85.9% specificity, 81.3% positive predictive value and 86.5% negative predictive value). Our results do not agree with those of Choe et al. who reported that CA 19-9 alone is suitable for the identification of PDAC in patients with new-onset DM. Our results are more consistent with those of Zubarik et al. who showed that the positive predictive value of CA 19-9 in patients with a positive family history of PDAC was only 3.7%.

The low sensitivity of US in our study suggests that it is not effective for screening. The effectiveness of abdominal CT in diagnosing PDAC was excellent in our study, but we could not prove that CT is an appropriate screening tool for early-stage PDAC. A limitation of our HiRiPaC study is the small number of cases, and we therefore planned to further investigate the possibilities of early detection of PDAC.

To identify a higher proportion of cases with resectable PDAC, the risk group of newly diagnosed DM patients should be further narrowed.

DM diagnosed in older individuals (>55 years) tends to be DM caused by PDAC, whereas diagnosis at a younger age is indicative of T2DM, as seen in our study. However, Gupta et al. came to the opposite conclusion: younger age is a risk factor for NOD-PDAC.

In the NODES trial we are studying elderly patients with new-onset diabetes mellitus using a biomarker panel (combining CA 19-9 with metabolites) to differentiate NOD-PDAC cases from T2DM patients. The expected positive endpoint of the NODES study is to validate this biomarker panel; whether it is suitable for early diagnosis of a mostly incurable, high mortality cancer, when surgery is still possible and the cancer can be cured. In this way, this biomarker panel could be a diagnostic tool for the T3cDM subset NOD-PDAC. The test requires only a single blood sample, which means it is simple, repeatable, tolerable, minimally invasive, almost painless, widely available and relatively inexpensive - it meets all the criteria for a screening method.

7. Conclusion

In conclusion, our prospective study demonstrated that the incidence of PDAC was significantly higher in patients with new-onset diabetes mellitus than in the normal population, making this group suitable for screening for PDAC. We confirmed that neither serum CA 19-9 nor transabdominal US, or both, are effective screening methods for the early detection of PDAC. In our study, abdominal CT is an effective imaging tool for the diagnosis of PDAC, but we were not able to prove that CT is an appropriate screening tool for early-stage PDAC.

The NODES study aims to validate a biomarker panel for the diagnosis of NOD-PDAC in elderly patients with new-onset diabetes, i.e. early detection of PDAC through surveillance of high-risk patients.

8. Novel observations

1. As statistically supported by our study, patients with new-onset diabetes mellitus are an appropriate group for pancreatic cancer screening.
2. CA 19-9 alone or in combination with transabdominal ultrasound is not effective for screening or diagnosing pancreatic ductal adenocarcinoma.
3. Transabdominal ultrasound is not effective for screening or diagnosing of pancreatic ductal adenocarcinoma.

4. Abdominal CT is a reliable imaging tool for the diagnosis of pancreatic ductal adenocarcinoma, although not in the early stages. It is therefore not suitable for screening, including radiation exposure.
5. By validating the biomarker panel studied in the NODES trial, the diagnosis of NOD-PDAC will allow us to screen for pancreatic ductal adenocarcinoma at an early stage in patients with new-onset diabetes mellitus.

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