PANCREATIC CANCER DETECTION USING METHYLATED DNA MARKERS IN PANCREATIC JUICE: A PROSPECTIVE MULTICENTER VALIDATION STUDY

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Abstract Body

Introduction

We have previously demonstrated that methylated DNA markers (MDMs) assayed from pancreatic juice (PJ) can detect early pancreatic ductal adenocarcinoma (PDAC). In this prospective multicenter study, we analyzed the diagnostic performance of MDMs in distinguishing PDAC from controls including those with chronic pancreatitis (CP) and intraductal papillary mucinous neoplasms (IPMNs).

Methods

Secretin-stimulated pancreatic juice was prospectively collected by endoscopic duodenal aspirate from January 2018 to August 2022 in 100 biopsy-proven treatment-naïve PDAC cases and 169 controls (normal healthy control: 71, disease controls: 98; CP: 29, IPMN: 69). From 850 µL of buffered PJ, 100 ng of bisulfite-converted DNA was analyzed for 14 MDMs (*NDRG4, BMP3, TBX15, C13orf18, PRKCB, CLEC11A, CD1D, ELMO1, IGF2BP1, RYR2, ADCY1, FER1L4, EMX1, LRRC4* and reference gene *B3GALT6*), by long-probe quantitative amplified signal (LQAS) assay. Random Forest (rFor) was used to train and cross-validate a model for predicting case/control status using all MDMs. Individual MDMs were ranked for their predictive importance within the cross-validated rFor model by randomly permutating MDM levels and estimating the impact on model prediction accuracy. Discrimination accuracy was measured using the area under the receiver operating characteristic curve (AUROC) with corresponding 95% confidence intervals. Logistic regression was used to assess performance of a 3-MDM panel comprising the most discriminant individual MDMs.

Results

Clinical and demographic characteristics are summarized in Table 1. Variable importance ranking indicated that *FER1L4, C13orf18, and BMP3* were the most discriminant individual PJ-MDMs for distinguishing cases from normal and disease controls matching our previously published results. Methylated *FER1L4* had the highest individual AUROC of 0.80 (0.74-0.86) and the AUROC for the 3-MDM panel (*FER1L4, C13orf18, and BMP3)* was 0.84 (0.79-0.89). The rFor model using all 14 MDMs had a

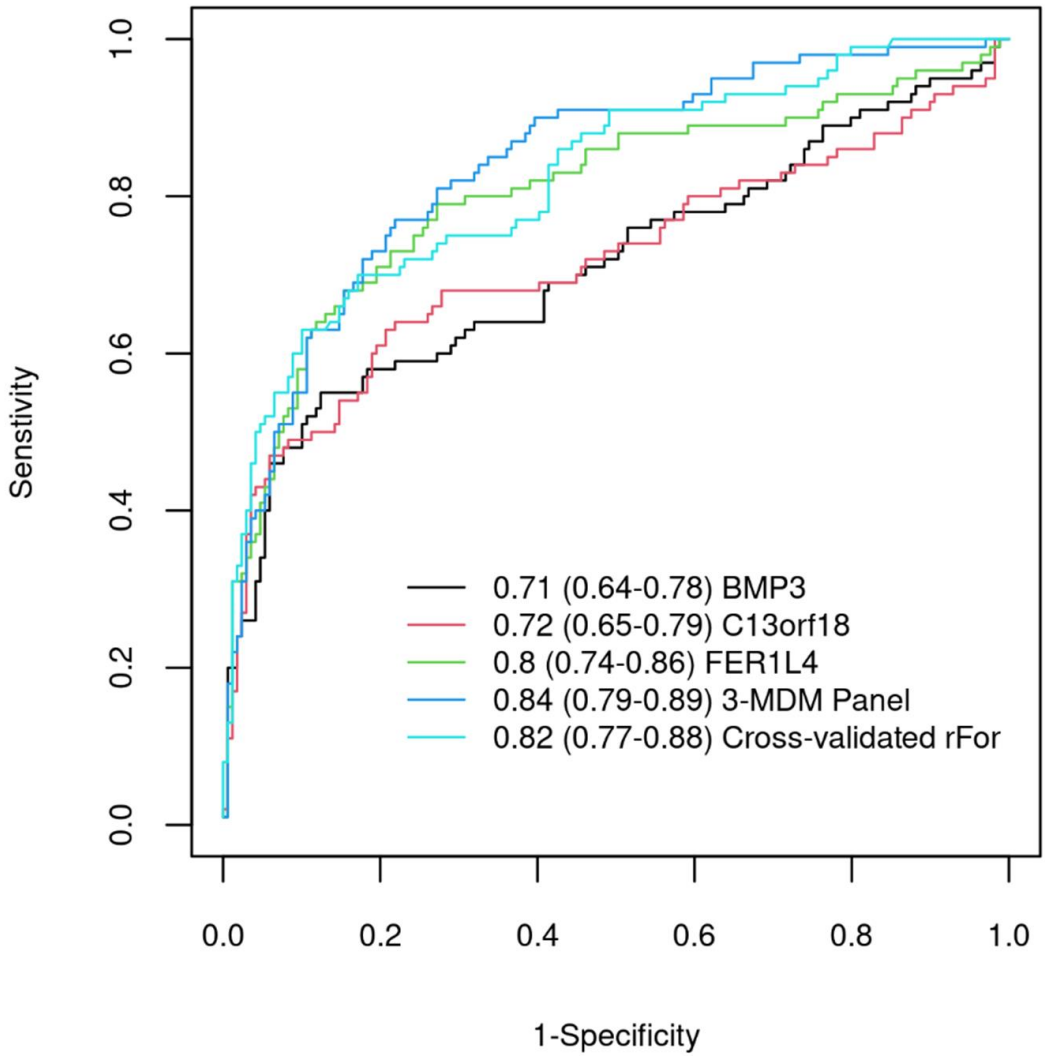
cross-validated AUC of 0.82 (0.77-0.88) (Figure 1). At an 80% specificity cut-off for the 3-MDM panel, the sensitivity for detecting any stage of PDAC was 73% (63-81%) and 65% (46-80%) for stage I/II PDAC. False positive rates in normal controls, CP, and IPMN patients were 8% (3-17%), 10% (2-27%), and 36% (25-49%), respectively.

Discussion

In a large prospective case-control study, we demonstrate that a PJ-MDM panel can distinguish PDAC from both normal and pancreatic disease controls with reasonable accuracy. Candidate MDMs with the highest variable importance for predicting PDAC in this study are identical to those reported previously providing justification for further assay optimization and clinical test development. Combining pancreatic juice MDMs with blood-based biomarkers may potentially further enhance diagnostic performance and serve as a tool for early detection of PDAC.

	Normal (N=71)	CP (N=29)	IPMN (N=69)	PDAC (N=100)
Age – *median (Q1, Q3)*	59 (48, 66)	59 (55, 67)	71 (64, 77)	71 (64, 77)
Sex – *Female (%)*	50 (70.4%)	15 (51.7%)	37 (53.6%)	54 (54.0%)
Tobacco – *n (%)*				
Missing	2	0	0	3
Current	13 (18.8%)	10 (34.5%)	5 (7.2%)	10 (10.3%)
Former	18 (26.1%)	8 (27.6%)	27 (39.1%)	45 (46.4%)
Never	38 (55.1%)	11 (37.9%)	37 (53.6%)	42 (43.3%)
Alcohol – *n (%)*				
Missing	6	0	3	7
Former	5 (7.7%)	9 (31.0%)	11 (16.7%)	22 (23.7%)
Less than 3x/week	22 (33.8%)	5 (17.2%)	24 (36.4%)	30 (32.3%)
More than 3x/week	7 (10.8%)	5 (17.2%)	14 (21.2%)	11 (11.8%)
Never	31 (47.7%)	10 (34.5%)	17 (25.8%)	30 (32.3%)
Diabetes – *n (%)*				
No	63 (88.7%)	19 (65.5%)	54 (78.3%)	67 (67.0%)
Yes: Type II	8 (11.3%)	8 (27.6%)	15 (21.7%)	30 (30.0%)
Yes: Unknown	0 (0.0%)	2 (6.9%)	0 (0.0%)	3 (3.0%)
FamHxPDAC – *n (%)*				
Missing	1	1	2	2
Yes	10 (14.3%)	2 (7.1%)	16 (23.9%)	10 (10.2%)
No	60 (85.7%)	26 (92.9%)	51 (76.1%)	88 (89.8%)
PDAC stage – *n (%)*				
	NA	NA	NA	
Stage I				12 (12.0%)
Stage II				22 (22.0%)
Stage III				26 (26.0%)
Stage IV				40 (40.0%)

CP: chronic pancreatitis; **IPMN**: intraductal papillary mucinous neoplasm; **PDAC**: pancreatic ductal adenocarcinoma; **Q1**: First quartile; **Q3**: Third quartile; **FamHxPDAC**: Family history of pancreatic ductal adenocarcinoma


Senstivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
0.71 (0.64-0.78) BMP3
0.72 (0.65-0.79) C13orf18
0.8 (0.74-0.86) FER1L4
0.84 (0.79-0.89) 3-MDM Panel
0.82 (0.77-0.88) Cross-validated rFor

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