

Supplementary Materials

Table S1. Sensitivity of individual markers at a fixed specificity for detecting early and overall pancreatic cancer using various control groups

Markers	Sensitivity (%) at a fixed specificity of 90%	Sensitivity (%) at a fixed specificity of 80%
S100A6		
EPC+LPC vs. H+CP	43.9 (38.2 - 49.7)	50.5 (44.9 - 61.5)
EPC+LPC vs. CP	24.6 (19.8 - 29.9)	52.8 (26.6 - 62.5)
EPC vs. H+CP	50.3 (42.0 - 58.6)	55.0 (47.6 - 65.1)
EPC vs. CP	26.2 (19.3 - 34.0)	56.4 (26.2 - 65.8)
CA19-9		
EPC+LPC vs. H+CP	66.1* (60.5 - 71.4)	74.4* (67.4 - 81.1)
EPC+LPC vs. CP	61.1* (55.4 - 66.7)	65.1* (58.1 - 73.4)
EPC vs. H+CP	63.1* (54.8 - 70.8)	73.8* (63.8 - 83.9)
EPC vs. CP	57.1* (48.7 - 65.1)	62.4* (53.0 - 72.5)
CEA		
EPC+LPC vs. H+CP	29.6 (24.5 - 35.1)	39.2 (29.2 - 52.8)
EPC+LPC vs. CP	21.9 (17.4 - 27.0)	29.6 (22.3 - 36.9)
EPC vs. H+CP	18.8	29.5

	(12.9 - 26.0)	(19.4 - 44.5)
EPC vs. CP	10.1 (5.7 - 16.1)	29.5 (14.8 - 46.6)

The values in () are 95% confidence intervals for sensitivity.

EPC, early pancreatic cancer; LPC, late pancreatic cancer; H, healthy control; CP, chronic pancreatitis; CI, confidence interval

*, highest sensitivity among three biomarkers

Table S2. Diagnostic accuracy of S100A6, CA19-9, and CEA for pancreatic cancer detection at optimal cutoffs

Markers	Cutoff*	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio	PPV (%)	NPV (%)	Accuracy (%)
S100A6								
EPC+LPC vs. H+CP	60.2 ng/mL	43.9	91.2	4.99	0.62	93.0	37.9	56.8
EPC+LPC vs. CP	44.0 ng/mL	52.8	80.8	2.75	0.58	94.1	22.8	56.9
EPC vs. H+CP	60.7 ng/mL	50.3	91.2	5.72	0.54	88.2	58.2	67.9
EPC vs. CP	49.3 ng/mL	55.0	82.7	3.18	0.54	90.1	39.1	62.2
CA19-9								
EPC+LPC vs. H+CP	37 U/mL	68.1	86.7	5.12	0.37	93.2	50.5	73.2
EPC+LPC vs. CP		68.1	73.1	2.53	0.44	93.6	28.4	68.8
EPC vs. H+CP		65.1	86.7	4.89	0.40	86.6	65.3	74.4
EPC vs. CP		65.1	73.1	2.42	0.48	87.4	42.2	67.2
CEA								
EPC+LPC vs. H+CP	4.7 ng/mL	25.9	92.0	3.24	0.81	89.7	31.8	44.0
EPC+LPC vs. CP		25.9	86.5	1.92	0.86	91.8	16.8	34.8

EPC vs. H+CP	14.1	92.0	1.76	0.93	70.0	44.8	47.7
EPC vs. CP	14.1	86.5	1.04	0.99	75.0	26.0	32.8

EPC, early pancreatic cancer; LPC, late pancreatic cancer; H, healthy control; CP, chronic pancreatitis; PPV, positive predictive value; NPV, negative predictive value

*, The cutoff values for CA19-9 and CEA were based on the manufacturer's guidelines for diagnosing pancreatic cancer, while the cutoff for S100A6 was determined using the maximum Youden's index in the ROC curves.

Table S3. Baseline characteristics between CA19-9-positive and CA19-9-negative but S100A6-positive pancreatic cancer patients

	High CA19-9 (≥ 37 U/mL)	Low CA19-9 & High S100A6 (< 37 U/mL) (≥ 60 ng/mL)	<i>P-value</i>
<i>N</i>	205	39	
<i>Age</i>	61 [52 - 68]	63 [52 - 69]	0.821
<i>Sex</i>			0.068
Male	115 (56.1)	28 (71.8)	
Female	90 (43.9)	11 (28.2)	
<i>Cancer histology type</i>			0.753
Ductal adenocarcinoma	193 (94.1)	37 (94.9)	
Neuroendocrine carcinoma	0 (0.0)	1 (2.6)	
Others*	12 (5.9)	1 (2.6)	
<i>TNM classification</i>			0.475
Stage I/II	2/95	1/21	
Stage III/IV	37/71	8/9	
<i>Underline DM</i>	82 (40.0)	16 (41.0)	0.905
<i>Smoking status</i>			
Ex-smoker	14 (6.8)	3 (7.7)	0.941
Non-smoker	132 (64.4)	24 (61.5)	

Smoker	59 (28.8)	12 (30.8)	
<i>Presence of other malignancy</i>	10 (4.9) [†]	2 (5.1) [‡]	0.947

* Histologic types other than pancreatic ductal adenocarcinoma and neuroendocrine tumor included acinar cell carcinoma, solid pseudopapillary neoplasm and others.

† The 10 malignancies are as follows; 3 gastric cancer, 3 breast cancer, 1 ovarian cancer, 1 prostate cancer, 1 lung cancer, and 1 thyroid cancer.

‡ The 2 malignancies are prostate cancer and laryngeal cancer, respectively.

Data are presented as numbers (%) for categorical variables or as medians [interquartile range] for continuous variables.

DM, diabetes mellitus

Table S4. Correlation coefficients among biomarkers

		Spearman's <i>r</i>	<i>P</i> -value
CA19-9	S100A6	0.18	<0.001*
S100A6	CEA	0.07	0.15
CEA	CA19-9	0.38	<0.001*

* statistically significant *P* value

Spearman's correlation coefficient is conventionally considered negligible when it's below 0.10, weak when it's between 0.10 and 0.39, moderate when it's between 0.40 and 0.69, strong when it's between 0.70 and 0.89, and very strong when it's above 0.90.

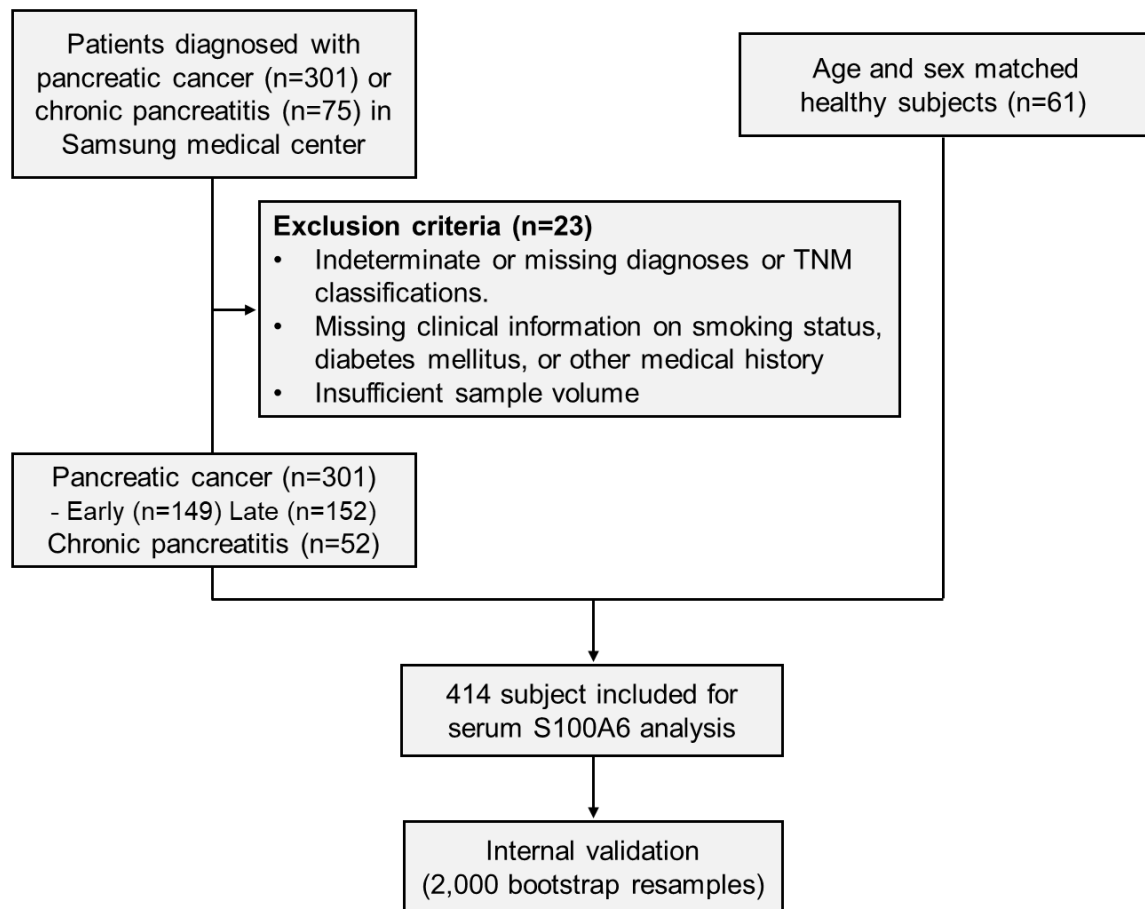


Figure S1. Flow chart of study population.

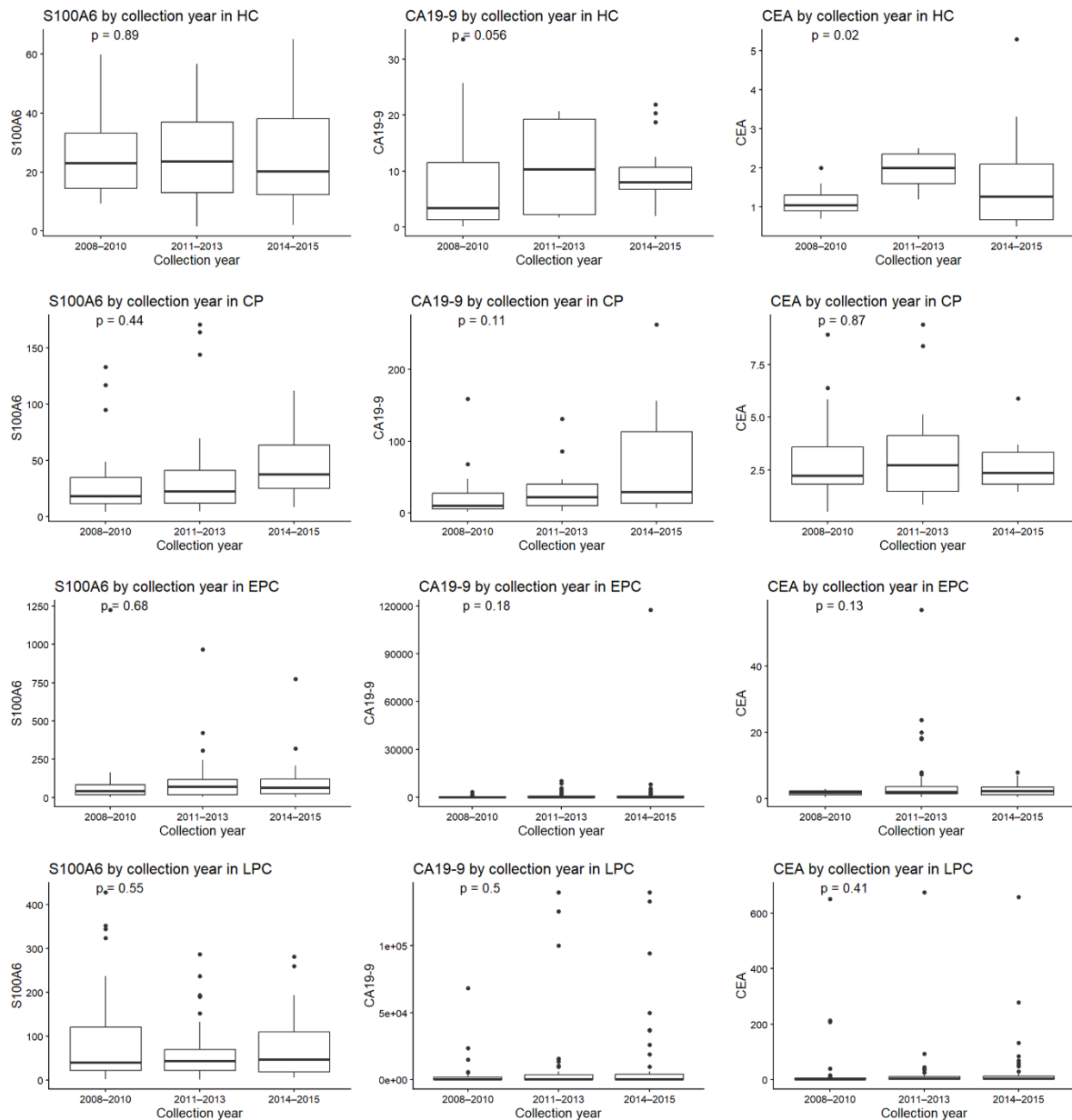


Figure S2 Biomarker concentrations across sample collection periods. S100A6, CA19-9, and CEA concentrations across three collection periods in healthy controls (HC), chronic pancreatitis (CP), early-stage PC (EPC), and late-stage PC (LPC). Box plots show median, interquartile range, and range. *P*-values from Kruskal-Wallis tests are shown. No temporal variation was observed for S100A6 or CA19-9 (all *P* > 0.05); CEA differed in HC (*P* = 0.02) but all values remained below the cutoff (4.7 ng/mL).

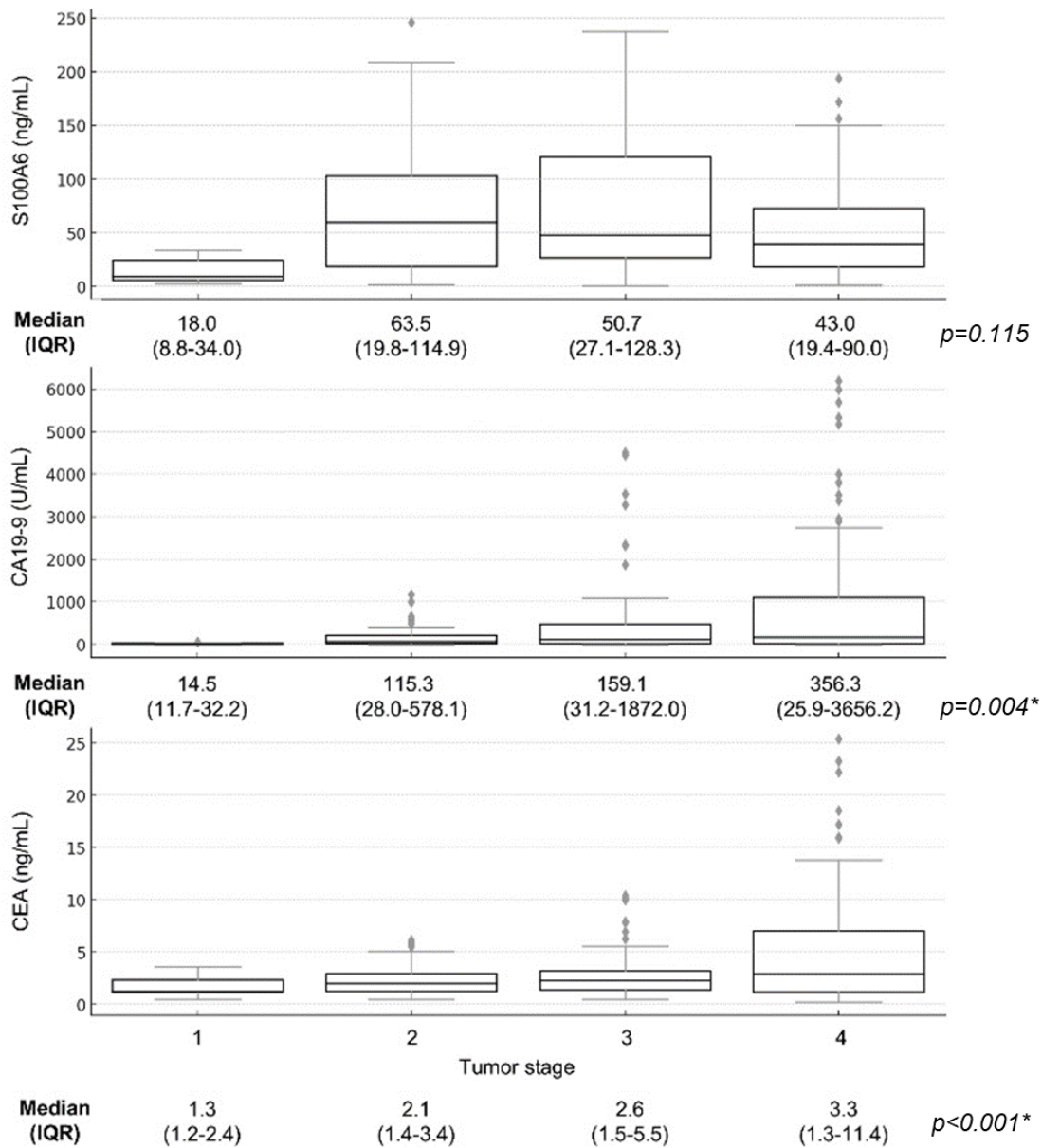


Figure S3 Stepwise comparison of concentrations of S100A6, CA19-9, and CEA according to tumor stage (n = 308): No significant difference in S100A6 concentrations was observed across stages using the Kruskal-Wallis test (Abbreviation: IQR, interquartile range) (* indicates a statistically significant *P*-value).