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Cystic fluid chromogranin A levels in different pancreatic cystic lesions

PANCREAS

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ABSTRACT

Background/Aims: Pancreatic cystic lesions have a broad spectrum of differential diagnosis. There is an ongoing demand to identify specific and sensitive cystic fluid markers for the differential diagnosis of pancreatic cysts. We aimed to evaluate the diagnostic value of cystic fluid chromogranin A (CgA) in the differential diagnosis of pancreatic cysts.

Materials and Methods: Patients who underwent endoscopic ultrasound (EUS)-guided aspiration for pancreatic cysts were included in the study. Cytopathological analysis and biochemical analysis, including cystic fluid carcinoembryonic antigen (CEA), amylase, Ca 19-9, and CgA, were performed.

Results: Fifty-three patients were included in the study. The final diagnosis of patients was 14 pancreatic pseudocysts, 10 intraductal papillary mucinous neoplasms (IPMNs), 8 mucinous cystic neoplasms (MCN), 8 serous cystadenomas (SCAs), 2 cystic pancreatic neuroendocrine tumors (PNETs), and 11 others. The mean CgA levels were 50.51±130.04 ng/mL in pseudocysts, 12.38±8.59 in MCN, and 13.76±10.90 in cystic PNET. There was only one patient with a very high cystic fluid CgA (515.49 ng/mL) and was diagnosed as pseudocyst developed in chronic pancreatitis patient. Two patients with cystic PNET had normal levels of cystic fluid CgA.

Conclusion: Cystic fluid CgA is not a useful marker for the differential diagnosis of cystic PNETs. It also has no value in the differential diagnosis of other pancreatic cysts.

Keywords: Chromogranin A, pancreatic cyst, cystic pancreatic neuroendocrine tumor, EUS

INTRODUCTION

Pancreatic cysts are generally detected during routine abdominal ultrasound or cross-sectional imaging studies (1). Pancreatic cystic lesions have a broad spectrum of differential diagnosis, including cystic neoplasms, solid neoplasms with cystic change, or non-neoplastic cysts. Although there is no gold standard test to discriminate pancreatic cystic lesions, clinical history, imaging findings, and cystic fluid cytopathological and biochemical analyses may help in differential diagnosis (2).

Endoscopic ultrasound (EUS) offers valuable information about pancreatic cysts (3,4). Using EUS-guided fine needle aspiration (EUS-FNA), it is possible to obtain pancreatic cystic fluid for cytopathological and biochemical analyses. Cystic fluid amylase, carcinoembryonic antigen (CEA) level, and deoxyribonucleic acid (DNA) molecular analysis might help in some cases to make a differential diagnosis (5). There is an ongoing demand to identify specific and sensitive cystic fluid markers for the differential diagnosis of pancreatic cysts.

Chromogranin A (CgA) is a soluble pro-hormone released by the neuroendocrine system or by cancer cells that can undergo neuroendocrine differentiation (6). Serum Cg A is the most widely accepted biomarker in pancreatic neuroendocrine tumors (PNETs) (7). The main reason for the increased circulating levels of CgA in patients with PNETs is that neoplastic cells release abnormal amounts of CgA, first into the tumor micro-

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environment and subsequently into the circulation (7). CgA is also reported to have important functions in angiogenesis, inflammation, and tissue repair (8,9).

Solid pancreatic tumors with cystic changes include solid pseudo-papillary tumor (SPT), pancreatic adenocarcinoma, and PNET (10). Cystic PNETs account for 13%–17% of PNETs in different series (11). We hypothesized that the level of cystic fluid CgA might increase in cystic PNETs as well as other pancreatic cystic lesions. However, there is no study in the literature evaluating the cystic fluid CgA levels in pancreatic cysts. In the present study, we evaluated the cystic fluid CgA levels and its potential as a diagnostic marker for a broad spectrum of pancreatic cystic lesions.

MATERIALS AND METHODS

Patients who were admitted to the pancreas outpatient clinic and were identified to have cystic pancreatic lesions between January 2011 and 2014 were evaluated. When EUS-FNA was indicated according to the current guidelines, the patient was included in the study (12). The study was approved by the local ethical committee, and informed consent was obtained from all patients before the procedures. Patients with endocrine disorders, diabetes, autoimmune disorders, chronic renal failure, cardiac failure, advanced liver failure, bleeding disorders, pregnancy, already diagnosed extrapancreatic malignancies, or neuroendocrine tumors were not included in the study. Patients who did not provide consent or had limited amount of cystic fluid that was obtained for analysis were also excluded.

Out of the 174 patients, 53 patients who underwent EUS-FNA for cystic pancreatic lesions were included in the study. Patient characteristics, including age, gender, associated symptoms, and medical history, were recorded. Relevant laboratory values, including serum CEA, Ca 19-9, and serum CgA levels, were recorded from medical records. EUS examinations were performed by two experienced gastroenterologist. Curvilinear echo-endoscopes (EG 530 UT Fujifilm, Japan or UCT180, Olympus, Center Valley, PA, USA with Hitachi Aloka Alpha 7 system, Tokyo, Japan) were used in EUS procedures. EUS characteristics of the cystic lesions, its location, and number were noted. EUS-FNA was performed with curvilinear echo-endoscopes, and standard 22 or 19 Gauge needles were used (Boston Scientific, Natick, MA, USA). The aspirated cystic fluid volume, color, and viscosity characteristics were noted. Cystic fluids aspirated by EUS-FNA were sent for cytopathological and biochemical analyses as well as CgA analysis.

Cytopathological evaluations were performed by experienced pathologists. Cytopathological slides and cell blocs were prepared. Slides were stained with hematoxylin and eosin or giemza. If required further immunohistochemical (IHC) staining were applied to the samples. Cystic fluid CEA, Ca19-9, and amylase levels were measured by an automated analyzer in the reference clinical biochemistry laboratory. Part of the cystic fluids were immediately frozen and stored at –80°C until CgA analysis. Cystic fluid CgA levels were measured by enzyme-linked immunosorbent assay (DIAsource Immuno Assays, Louvain-la-Neuve, Belgium), as described. In brief, the assay utilizes the two-site "sandwich" technique with two selected antibodies that bind to different epitopes of human CgA. Assay calibrators, controls, and patient samples are directly added to the microtiter wells of a microplate coated with a polyclonal anti-chromogranin A antibody. After the described steps, a calibration curve is generated. The concentration of human CgA in test samples is directly determined from this calibration curve.

After cytopathological and biochemical analyses, final diagnosis were reported and patients were advised according to current guidelines (13). Pancreatic cyst types were also grouped for data analysis in the following way: non-neoplastic cysts, mucinous neoplastic cysts, non-mucinous neoplastic cysts, or cystic degeneration of tumors. For statistical analysis, IBM SPSS 20.0 statistical package (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA) was used. Statistical analysis included parametric tests, non-parametric tests of comparison, one-way analysis of variance (ANOVA), and receiver operating characteristic (ROC) curve analyses. $p<0.05$ was considered as statistically significant.

RESULTS

We evaluated 174 patients with pancreatic cysts who were admitted to the outpatient clinic between 2011 and 2014, and 53 patients (20–74 years, 51.7±14.8 years, 21 M, 32 F) were further evaluated with EUS-FNA for diagnostic purposes or worrisome features according to the guidelines.

Table 1. Demographic features of study group

	Number	Age (Mean±SD) years	Gender (M/F)	Serum Ca19-9 (u/mL)	Serum CEA (ng/mL)
Pseudocyst	14	53.6±12.3	8/6	14.44±14.32	1.95±0.81
IPMN	10	51.8±16.6	6/4	15.44±18.07	1.89±1.10
MCN	8	55.3±19.1	0/8	24.44±23.14	1.86±0.74
SCA	8	43.1±11.8	1/7	18.57±10.97	2.13±0.87
Cystic Pancreatic Cancer	4	62.7±9.6	2/2	681.37±455.48	17.42±27.58
Simple cyst	4	44.0±14.7	2/2	15.25±19.29	2.81±1.51
SPT	2	38.5±2.1	1/1	3.74±2.60	0.94±0.08
Cystic PNET	2	68.0±5.6	1/1	16.70±8.48	2.91±0.15
Acinar cell cystadenom	1	44.0±0.0	0/1	6.70±0.00	0.38±0.00
Total	53	51.7±14.8	21/32	70.51±216.90	3.27±8.24

IPMN: intraductal papillary mucinous neoplasms; MCN: mucinous cystic neoplasms; SCA: serous cystadenomas; PNET: pancreatic neuroendocrine tumors; SPT: solid pseudo-papilllary tumors; CEA: carcinoembryonic antigen; M/F: male/female; SD: standard deviation

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Table 2. Cystic fluid chromogranin A (CgA), Amylase, arcinoembryonic antigen (CEA), Ca19-9 levels in different pancreatic cystic lesions

	CgA (ng/mL) (Mean±SD)	Amylase (u/L) (Mean±SD)	CEA(ng/mL) (Mean±SD)	Ca19-9 (U/mL) (Mean±SD)
Pseudocyst (n14)	50.51±134.04	27181.00±48836.44	25.32±56.16	2682.13±7686.10
IPMN (n10)	8.79±5.37	41624.20±53770.80	974.53±2615.25	35869.41±57386.57
MCN (n 8)	12.38±8.59	731.25±1547.64	12088.85±26195	61122.16±138042.22
SCA (n8)	9.88±10.14	262.50±234.16	0.47±0.62	1269.85±1217.81
Cystic Pancreatic Cancer (n4)	9.44±1.05	7407.50±10447.50	22493.82±20506.02	117071.90±191264.22
Simple cyst (n4)	8.63±2.18	447.60±89.23	1.28±1.28	3414.87±5708.43
SPT (n2)	11.66±5.10	206.50±258.09	5.45±7.42	72.75±65.27
Cystic PNET 2	13.76±10.90	562.50±719.12	61.64±83.94	200019.9±282814.49
Acinar cell cystadenom (n1)	21.4±0.0	913.90±0.00	32.42±0.00	30342.00±0.00

IPMN: intraductal papillary mucinous neoplasms; MCN: mucinous cystic neoplasms; SCA: serous cystadenomas; PNET: pancreatic neuroendocrine tumors; SPT: solid pseudopapilllary tumors; CgA: Chromogranin a; CEA: carcinoembryonic antigen; SD: standard deviation

Table 3. Pancreatic cystic lesions grouped as non-neoplastic cysts, neoplastic mucinous cysts, neoplastic nonmucinous cyst and cystic degeneration of pancreatic cancer

	CgA (ng/mL) (Mean±SD)	Amylase (u/L) (Mean±SD)	CEA (ng/mL) (Mean±SD)	Ca19-9 (U/mL) (Mean±SD)
Non-neoplastic (n18)	41.20±118.58	31088±57320	21.08±51.50	2811.44±7221.88
Neoplastic mucinous (n18)	10.39±7.00	23449.56±44371.83	5914.22±17845.45	47092.86±98775.67
Neoplastic non-mucinous (n13)	11.63±9.10	351.31±350.538	13.10±33.64	33898.94±110304.55
Cystic pancreatic cancer (n 4)	9.44±1.05	7407.50±10447.50	22493.82±20506.02	117071.90±191264.22

CgA: Chromogranin a; CEA: carcinoembryonic antigen; SD: standard deviation

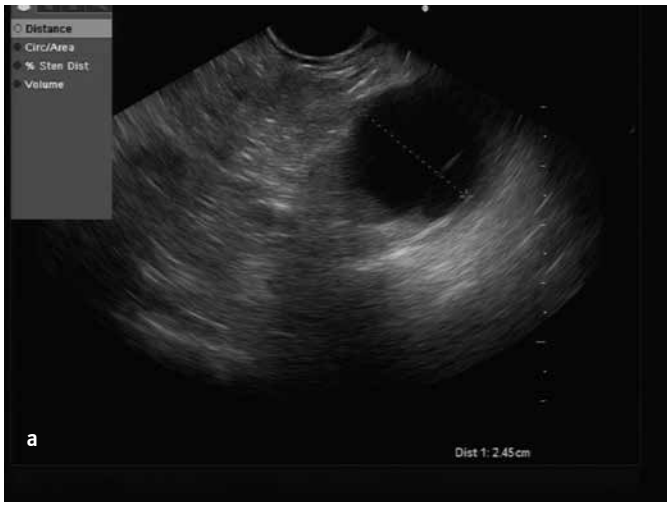
Patient characteristics, including age, gender, associated symptoms, and medical history, were noted. Relevant laboratory values, including serum CEA and serum Ca19-9 levels, were recorded from medical records. None of the patients had initial serum CgA measurements. Pancreatic cystic lesions in subjects were diagnosed as pseudocysts (n14), intraductal papillary mucinous neoplasms (IPMN) N (n10), mucinous cystic neoplasms (MCN) (n8), serous cystadenomas (SCA) (n8), cystic PNET (n2), SPT (n2), cystic degeneration of pancreatic cancer (n2), acinar cell cystadenom (n1), and simple cysts (n4) (Table 1). The mean age of the patients was similar between the groups with different pancreatic cystic lesions. SCA and MCN were only observed in females, whereas gender distribution in other groups were similar ($p<0.05$). Serum Ca19-9 levels were significantly higher in the cystic degeneration of pancreatic cancer than in other groups ($p<0.001$). Moreover, serum CEA was higher in that group than in others, but the difference was not significant.

When we compared cystic fluid CgA levels between different pancreatic cyst types, there were no significant differences between the groups (Table 2). Cystic fluid CgA level did not correlate with the patient's age, cyst diameter, cystic CEA, or Ca19-9 levels. However there was a weak positive correlation between cystic CgA and amylase levels ($p<0.05$, r:0.31).

Cystic fluid amylase levels were higher in pseudocysts and IPMN, but the difference was not significant. Cystic fluid CEA levels were higher in cystic degeneration of pancreatic cancer and MCN then in other groups ($p<0.05$). Cystic fluid Ca19-9 levels were similar between the different cyst types.

Two patients were diagnosed to have cystic PNETs. On EUS examination, one of these patients had slightly thickened cystic wall. However, none of the other EUS findings was specific and diagnostic (Figure 1 a,b). Cytopathology was diagnostic in one cystic PNET patient and non-diagnostic in the other (Figure 1 c,d). Both of the cystic PNET patients had low level of cystic fluid CgA. Mean CgA levels were 13.76±10.90 ng/mL in cystic PNETs. In contrast, their serum mean CgA levels were high (192 ng/mL and 1430 ng/mL, respectively). Cystic fluid CgA level over 10 ng/mL was 41% sensitive and 50% specific for diagnosis of cystic PNETs (AUC 0.46).

There was only one patient with very high cystic CgA (515.49 ng/mL) level and was diagnosed as pseudocyst that developed in the background of chronic pancreatitis. This patient had very high cystic amylase level (119754 U/L, low cystic CEA (5.1 ng/mL) and Ca 19-9 (2 U/mL) levels. When the patient was further evaluated, his serum CgA level was found to be normal (51.40 ng/mL), and gallium-68 DOTATATE positron emission tomography (Ga-68 DOTATATE PET/CT) was also found to be negative.
When patients were grouped according to their diagnosis as cystic degeneration of neoplastic tumors (including SPT,



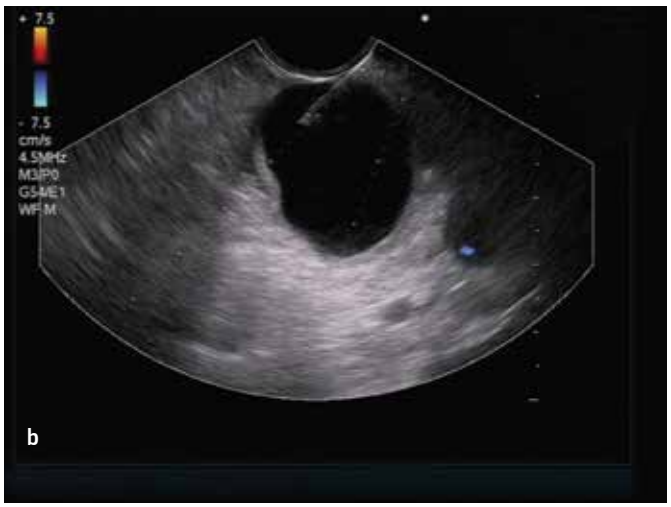
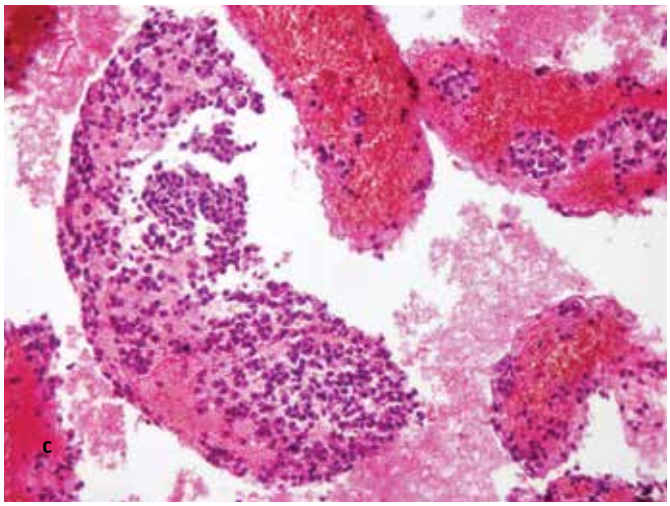


Figure 1. a,b. Cystic PNET with asymmetrically thickened Wall (a), EUS-FNA application to cystic PNET with 22 G needle (b).



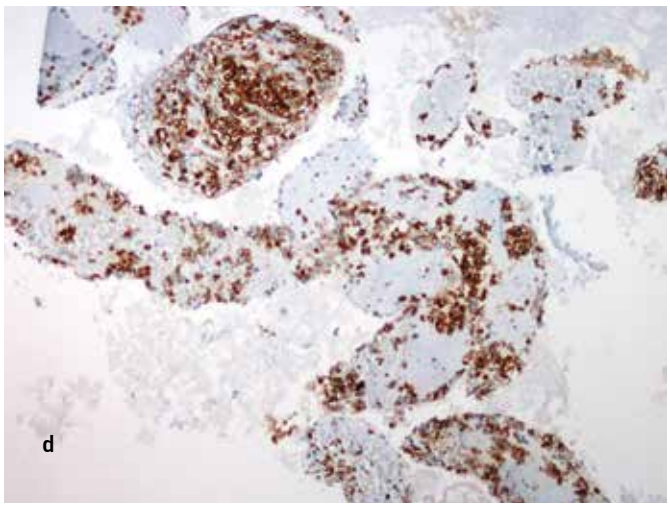


Figure 1. c,d. Cytopathology shows PNET (HE x100) (c), chromogranin A was positive by IHC in cystic PNET. (x100) (d).

pancreatic cancer, and cystic PNET), non-neoplastic pancreatic cysts, mucinous neoplastic cysts, and non-mucinous neoplastic cysts, the mean cystic CgA levels were 11.07±4.98, 41.20±118.58, 10.39±7.00, and 11.16±10.23, respectively. The difference was not significant. Similarly, when patients are grouped as non-neoplastic pancreatic cysts, mucinous neoplastic cysts, and non-mucinous neoplastic cysts, there was no significant difference between the cystic fluid CgA levels of the groups (Table 3).

DISCUSSION

Pancreatic cystic lesions have a broad spectrum of differential diagnosis, including pseudocysts, IPMN, MCN, SPT, SCA, ductal adenocarcinoma with cystic degeneration, cystic PNET, simple cyst, and acinar cell cystadenoma. EUS is very helpful in visualizing pancreatic cystic lesions and obtaining cystic fluid for further analysis. Currently, the measurement of cystic amylase and CEA are most routinely used in clinical practice (14). There has been an increasing interest to determine the specific and sensitive pancreatic cyst biomarkers to differentiate between the different cyst subtypes.

Clinical history of pancreatitis, imaging findings, and high cystic fluid amylase level are helpful in the diagnosis of pseudocyts. Pancreatic cystic lesion related to pancreatic duct may suggest IPMN. Cystic lesion located in the tail of the pancreas with high mucionus cystic content and high CEA is usually relevant to MCN.

Cystic PNETs are a rare entity that causes diagnostic challenge (15). In an asymptomatic patient, if CT reveals a cystic pancreatic lesion with thick cyst wall and hypervascular margins, it supports the diagnosis of cystic PNET. Kongkam et al. could not identify any unique endoscopic ultrasound finding in cystic neuorendocrine tumors (16). IHC usually demonstrates strong staining for chromogranin A and in that case cytopathology may be diagnosed (17). Cystic fluid amylase and CEA levels are usually low in PNETS compared with other cysts (18http://www.sciencedirect.com/science/article/pii/S1072751508000240 - bib2,19). In our study, we diagnosed two patients with cystic PNETs. One male patient had cystic PNET with thickened wall, and cytopathology was diagnostic. The second patient had pure cystic lesion, and EUS-FNA was non-diagnostic and histopathology confirmed cystic PNET. In

our study, both cystic PNET patients had low cystic CEA and amylase levels.

CgA is a soluble circulatory pro-hormone. It is used to determine tumor burden, prognosis, treatment response, or recurrence in PNETs (20,21). CgA is mainly secreted by neuroendocrine cells. Although plasma CgA is the most widely used biomarker in the diagnostic workup and follow-up of pancreatic neuroendocrine neoplasms, there is no study investigating the role of cystic fluid CgA in pancreatic cysts, particularly in cystic PNETs. There is only one case report in the literature suggesting that cystic fluid CgA is helpful in diagnosis of pancreatic cystic PNETs. In that case report, Maletta et al. (22) reported a patient with pancreatic cyst with a suspicion for PNET. Cyst fluid analysis showed high levels of CgA, which was 138 ng/mL (normal range 20–100ng/mL), whereas amylase and CEA were low. Patient was operated, and final histopathological diagnosis confirmed cystic PNET. Authors suggested that cystic fluid CgA can be a useful diagnostic tool in preoperative diagnosis of cystic PNET, particularly in those cases where EUS-FNA provides little material for traditional cytological and IHC investigations. However in our cystic PNET patients, the cyst fluid levels of CgA were normal, while their circulating Cg A levels were high. This difference may be the results of different nature of pancreatic cystic PNETS. CgA IHC positivity is 80% in cystic PNETS (23,24). This means some cystic PNETs may not express CgA. However, in our study, both cystic PNETs were positive for IHC CgA and had high circulating CgA levels. We may speculate that PNETs secrete CgA by exocytosis directly into the circulation and not in the cystic fluid. Second assumption is that cystic PNETs arise because of tumor necrosis within solid PNETs, and in degenerative cystic fluid, CgA level may decrease or fluctuate by time (25).

In our study, there was only one patient with very high cystic CgA (515.49 ng/mL) level. This patient had high cystic amylase level, low cystic CEA and Ca 19-9 levels, and normal serum CgA level. Meticulous investigations showed that this case was not a PNET, and its final diagnosis after surgery was chronic pseudocyst that developed in chronic pancreatitis. Pseudocysts, retention cysts, lymphoepithelial cysts, and benign epithelial cysts are non-neoplastic cysts (26). When we grouped those lesions together, the mean CgA level was slightly higher in those groups compared with neoplastic cysts. CgA is reported to have important functions in angiogenesis, inflammation, and tissue repair (8,9). CgA is also released from immune system by activated leucocytes (27). Fragments of CgA have some anti-inflammatory and antifungal activities (27). The slightly higher levels of CgA in particularly infected pseudocyts may be because of reactive leucocytes activation in pseudocyst. The prognostic value of cystic fluid and serum CgA levels in pancreatitis patients should be evaluated in further studies.

This study is the first study in the literature investigating the cystic CgA levels in broad spectrum of pancreatic cystic lesions. However, there are some important limitations in our study. First, our study is subject to selection bias given that only patients who underwent EUS-FNA were included in the study. Therefore, those patients represent a subset of the population whose lesions were, at baseline, concerning or atypical. Therefore, our results may not reflect all patients with pancreatic cysts. Second, some subsets of study groups were small because some cystic lesions, including cystic PNETs, SPT, or acinar cell cystadenoma, were very rare. Another limitation of this study is that there is usually no indication for EUS-FNA for pseudocysts. EUS-FNA was performed on atypical pseudocysts without clear history of pancreatitis or during EUS-guided cystogastrostomy. Finally, although we measured cystic CgA levels, we did not measure serum CgA levels of all patients for comparison and correlation analyses. Further studies may evaluate the serum profile of CgA in different pancreatic disorders.

In conclusion, we showed that pancreas cystic CgA level is not a good diagnostic biomarker with low sensitivity and specificity. Cystic fluid CgA is not useful for differential diagnosis of cystic PNETs and also has no value in differential diagnosis of other pancreatic cysts. The prognostic significance of CgA level in pseudocysts warrants for further investigation.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.O., A.A., B.B.; Design - N.O., B.B., C.A.; Supervision - A.A., A.V.; Resource - N.O., D.N., B.B.; Materials - N.O., A.A., B.B.; Data Collection and/or Processing - B.B., C.A., D.N.; Analysis and/or Interpretation - N.O., B.B., C.A.; Literature Search - N.O., C.A.; Writing - N.O., C.A.; Critical Reviews - N.O., A.A., A.V.

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