의학박사 학위논문

췌장 낭성질환에서 흡인액의 감별진단에 대한 임상 결과 분석

Clinical impact of cystic fluid analysis for differential diagnosis of pancreatic cystic lesions

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이 논문을 의학박사 학위 논문으로 제출함

2024 년　2 월

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Abstract

Background and Aims: Accurately diagnosing pancreatic cystic lesions (PCLs) using only radiological tools is challenging. Measuring cystic carcinoembryonic antigen (CEA) and glucose levels could be helpful in the differential diagnosis of mucinous neoplastic pancreatic cysts (MNPCs) from non-MNPC. Herein, the diagnostic role of cystic fluid analysis in therapeutic decision-making for PCLs was evaluated.

Methods: Data were retrospectively collected from patients who underwent cystic fluid analysis before pancreatic surgery for PCLs or through the needle biopsy (TTNB) between January 2006 and December 2021. The diagnostic values of cystic CEA and glucose levels for differential diagnosis of PCLs were analyzed.

Results: In total, 352 patients were included in the analysis. Of these, 264 had MNPCs and 88 had non-MNPCs. The area under the receiver operating characteristic (AUROC) curve for CEA levels in differentiating MNPC from non-MNPC was 0.866 (95% confidence interval (CI): 0.816–0.916, P <0.01) with a cut-off of 8.8 ng/mL, demonstrating a sensitivity and specificity of 91.3% and 75%, respectively. With the most commonly used cutoff value of 192 ng/mL, the AUROC was 0.718 (95% CI: 0.674–0.762, P <0.001), with sensitivity and specificity of 53.8% and 87.9%, respectively. Glucose alone or combining glucose and/or CEA did not show better diagnostic performance than CEA alone.

Conclusions: Owing to varying cutoff values in different studies and sub-optimal diagnostic accuracy, the use of cystic CEA or glucose should be limited to a supplementary role. Therefore, it is essential to explore new diagnostic markers for cystic fluid to enhance diagnostic precision.

Keywords: Pancreas; Cyst; Neoplasm; CEA; Glucose

목 차

표 및 그림 목차

Introduction

The diagnosis of pancreatic cystic lesions (PCLs) is rising with increased detection via abdominal imaging,[1] especially in the healthcare check-up system for asymptomatic individuals in South Korea.[2] PCL is largely divided into non-neoplastic and neoplastic cysts; neoplastic cysts are differentiated into mucinous or non-mucinous cystic neoplasms.[3,4] Generally, mucinous neoplastic pancreatic cysts (MNPCs) are managed as premalignant lesions, which may require surveillance or surgery. In contrast, non-MNPCs are primarily not premalignant lesions that usually do not require surveillance or treatment. Therefore, several imaging modalities, including computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS), are used for accurate diagnosis. However, a specific diagnosis is challenging, as many cysts lack distinctive imaging features other than their location or size. The accuracy of CT and MRCP for the diagnosis of specific types of cysts is 40–50%.[5] EUS without fine-needle aspiration (FNA) may provide additional information regarding the evaluation of mural nodules; however, the accuracy is similar to that of MRCP or CT.[4] Owing to low accuracy, some patients may undergo unnecessary follow-up tests or surgery. Cyst fluid analysis has been suggested as a useful marker to overcome the low accuracy of imaging modalities. Brugge et al.[6] reported that the cyst fluid carcinoembryonic antigen (CEA) level is the most accurate marker for the diagnosis of mucinous cystic lesions of the pancreas. However, its role remains controversial. To improve diagnostic accuracy, through the needle biopsy (TTNB) or confocal endomicroscopy have been introduced.[7] TTNB has shown good performances. However, the steps are not standardized and are complex compared cystic fluid analysis alone. It is unclear whether cystic fluid analysis plays a role in the differential diagnosis of PCLs in the era of TTNB. Therefore, we aimed to present real-world data regarding the accuracy of fluid analysis for the differential diagnosis of MNPC using histopathological results from surgery and TTNB.

Methods

1. Study design

We reviewed the database of patients who underwent cystic fluid analysis before pancreatic surgery or TTNB between January 2006 and December 2021 in our center. Baseline characteristics of the patients (age, sex), location and size of the cystic neoplasm, and pathologic diagnosis were collected and analyzed. This study was approved by the Institutional Review Board of Asan Medical Center (approval no. 2023-0797). This study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

2. Definition and outcome

MNPCs were defined as either intraductal papillary mucinous neoplasms (IPMNs) or mucinous cystadenoma (MCNs). The other patients were considered to have non-MNPCs. The primary outcome was the diagnostic values of cystic CEA and glucose levels in the differential diagnosis of PCLs. As 192 ng/mL is the most commonly used as the optimal CEA cutoff level, its diagnostic value was also analyzed.[3,4] A receiver operating characteristic (ROC) curve was also obtained for the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

3. Endoscopic procedure

EUS-FNA was performed using a conventional linear-array echoendoscope (GF-UCT 260; Olympus Optical, Tokyo, Japan). After careful evaluation of the cystic neoplasm, a 19-gauge needle (EUSN-19-T; Cook Endoscopy, Winston-Salem, NC, USA) was used to aspirate the cystic fluid. Microforceps (Moray Microforceps; US Endoscopy, Mentor, Ohio, USA) were used for TTNB after aspiration of the cystic fluid.

4. Statistical analyses

The baseline characteristics and clinical outcomes of the patients are presented as means, standard deviations, medians, ranges, or percentages, as appropriate. The diagnostic performance of CEA and glucose levels to diagnose MNPC versus non-MNPC was assessed using ROC curves. The optimal cut-off values were selected for the maximum area under the ROC (AUROC) curve. The sensitivity, specificity, positive PPV, and NPV of CEA and glucose levels were calculated using R v3.5.3. (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Results

1. Patient characteristics

During the study period, 352 patients were included, with 196 diagnosed by surgery and 156 by TTNB (Fig. 1). The baseline characteristics of the patients are summarized in Table 1.

Figure 1. Flow chart of the study

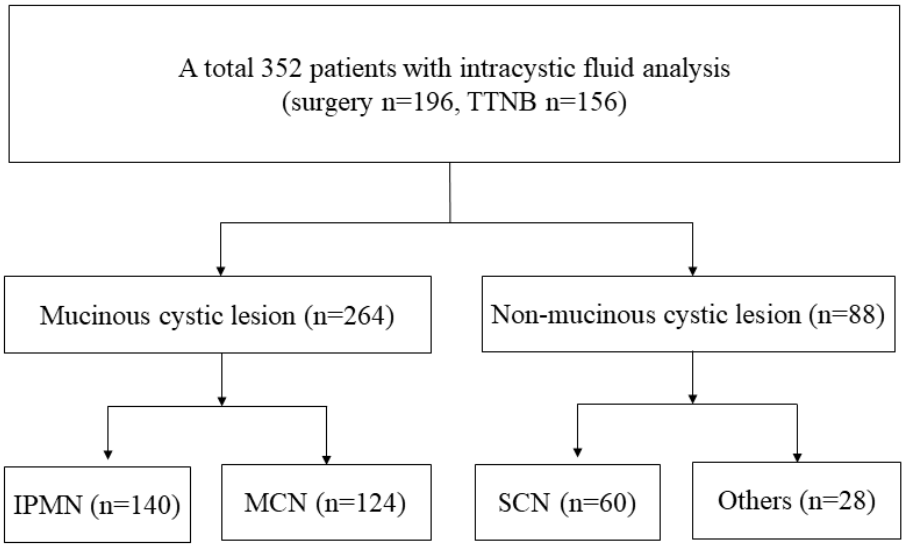


Table 1. Baseline characteristics of the patients

Characteristics	Total (n = 352)	MNPCs (n = 264)	Non-MNPCs (n = 88)	P-value
Female	246 (67.8)	182 (68.9)	57 (64.8)	0.553
Age	55.5 ± 14.2	57.2 ± 14.4	50.5 ± 12.6	<0.001
Location				0.946
Head and uncinate	101 (28.7)	75 (28.4)	26 (29.5)	
Body and tail	251 (71.3)	189 (71.6)	62 (70.5)	
Cyst size, mm	40.0 ± 17.8	39.9 ± 17.9	40.4 ± 17.4	0.801

All values are presented as numbers (percentages) or means (standard deviations).

MNPCs, mucinous neoplastic pancreatic cysts

2. Pathology diagnosis

MNPCs was diagnosed in 264 patients (160 via surgery and 104 via TTNB). In total, 124 patients were diagnosed with MCN, and the remaining 140 were diagnosed with IPMN. Eighty-eight patients had non-MNPCs (60 serous cystadenomas (SCN), seven retention cysts, six epidermoid cysts, four neuroendocrine tumors (NET), three pseudocysts, three cystic lymphangiomas, two lymphoepithelial cysts, one polycystic kidney disease, one squamoid cyst, and one foregut cyst).

3. Cystic CEA level

For the 352 patients, the median CEA level was 85.7 ng/mL (range 0.3–3323720.0). Median CEA levels in MNPCs and non-MNPCs were 252.6 ng/mL (range 0.3–3323720) and 1.73 ng/mL (0.4–10965), respectively (Fig. 2A). The AUROC curve for CEA levels in distinguishing between MNPCs and non-MNPCs was 0.866 (95% confidence interval (CI): 0.816–0.916, P <.01) with a cut-off of 8.8 ng/mL, demonstrating a sensitivity and specificity of 91.3% and 75%, respectively (Fig. 2B). With the currently recommended cut-off value of 192 ng/mL, the AUROC was 0.718 (95% CI, 0.674–0.762, P <0.001), with a sensitivity and specificity of 53.8% and 87.9%, respectively (Tables 2 and 3).

4. Cystic glucose level

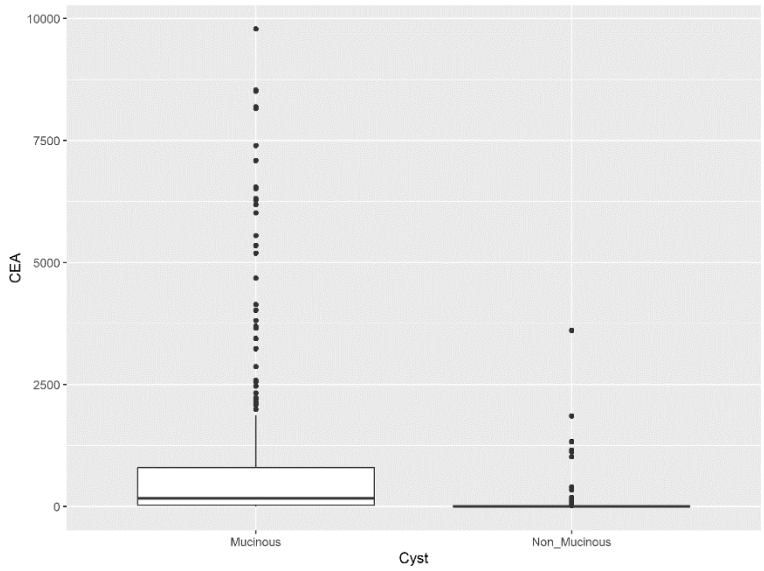
Of the 352 patients, 103 had cystic glucose levels (50 IPMN, 20 MCN, 24 SCN, four retention cysts, one NET, two epidermoid cysts, one polycystic kidney disease, and one lymphoepithelial cyst). The AUROC for glucose levels in distinguishing between MNPCs and non-MNPCs was 0.755 (95% CI: 0.648–0.861, P <.01) with a cut-off of 40 mg/dL, demonstrating a sensitivity and specificity of 94.3% and 50%, respectively. (Tables 2 and 3).

5. Combining CEA and glucose

With 103 patients having CEA and glucose measurements, the combination of either CEA (≥8.8 ng/mL) or glucose (≤40 mg/dL) yielded an AUROC of 0.758 (95% CI: 0.671–0.844, P = 0.01) with 100% sensitivity and 51.5% specificity. Satisfying both CEA (≥8.8 ng/mL) and glucose (≤40 mg/dL) criteria results in an AUROC of 0.823 (95% CI: 0.743–0.904, P = 0.383) with 82.9% sensitivity and 81.8% specificity (Table 3).

Figure 2. (A) Boxplot of cystic CEA concentration in MNPCs and non-MNPCs (B) Receiver operating characteristic curve with a cut-off of 8.8 ng/mL.

(A)



(B)

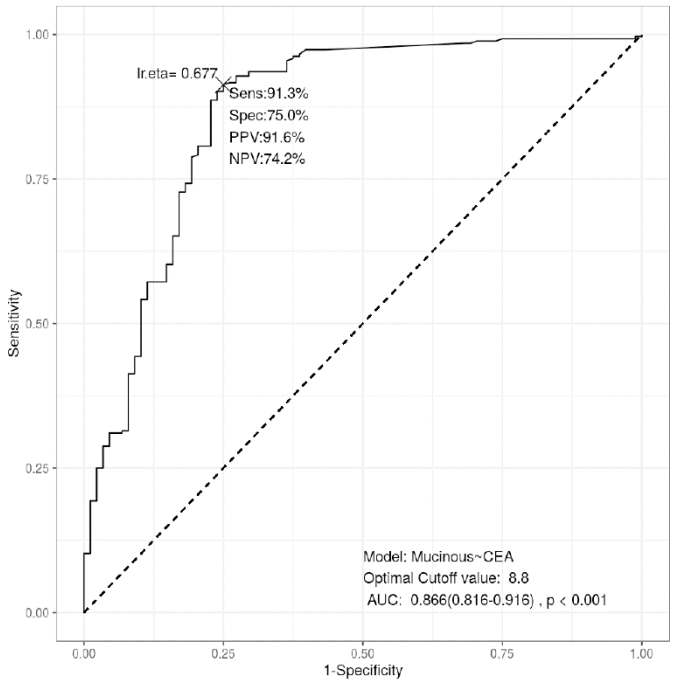


Table 2. CEA and glucose concentration via histologic diagnosis

	Fluid diagnostic test	
Histologic diagnosis	CEA, ng/mL	Glucose*, mg/dL
MNPCs (n = 264)	252.6 (0.3–3323720)	2.0 (2.0–74.0)
IPMNs (n = 140)	92.2 (1.6–2564700)	2.0 (2.0–40.0)
MCNs (n = 124)	696.5 (0.3–3323720)	9.5 (2.0–74.0)
Non-MNPCs (n = 88)	1.73 (0.4–10965)	30.0 (2.0–144.0)
Serous cystic neoplasms (n = 60)	1.73 (0.4–1333.2)	80.5 (2.0–144.0)
Neuroendocrine tumor (n = 4)	1.8 (0.9–5.8)	109
Others (n = 24)	34.7 (0.5–10965)	2.0 (2.0–9.0)

All values are presented as medians (range).

CEA, carcinoembryonic antigen; IPMNs, intraductal papillary mucinous neoplasms; MCNs, mucinous cystic neoplasms; MNPCs, mucinous neoplastic pancreatic cysts

*103 patients (50 IPMNs, 20 MCNs, 24 SCNs, one NETs, and nine others) whose glucose levels were analyzed.

Table 3. Accuracy of CEA and glucose to differentiate MNPCs and non-MNPCs

	Cut-off value	AUC	95%CI	P value	Sensitivity	Specificity	PPV	NPV
CEA	>8.8	0.866	0.816–0.916	<0.001	91.3	75	91.6	74.2
	>192	0.718	0.674–0.762	<0.001	53.8	89.8	94	39.3
Glucose*	<40	0.755	0.648–0.861	<0.001	94.3	51.5	80.5	81
CEA or glucose positive*	>8.8 or <40	0.758	0.671–0.844	0.01	100	51.5	81.4	100
CEA and glucose positive*	>8.8 and <40	0.823	0.743–0.904	0.383	82.9	81.8	90.6	69.2

*103 patients (50 IPMN, 20 MCN, 24 SCN, four tension cysts, one NET, tow epidermoid cysts, one PKD, and one lymphoepithelial cyst) whose glucose results were analyzed.

AUC, area under the curve; CEA, carcinoembryonic antigen; CI, confidence interval; dL, deciliter; mg, milligram; mL, milliliter; ng, nanogram; NPV, negative predictive value; PCN, pancreatic cystic neoplasm; PPV, positive predictive value

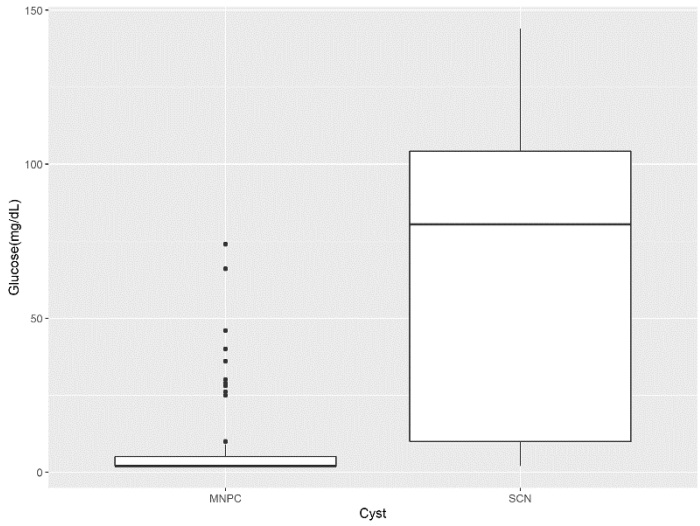
6. Secondary outcomes

Cystic glucose for differentiating SCN from MNPCs

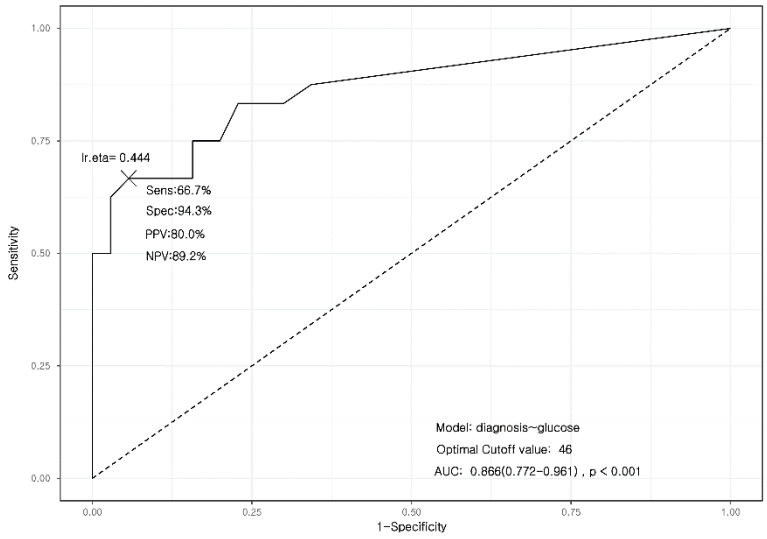
Cystic glucose levels were also evaluated to distinguish SCN (n = 24) from MNPCs (n = 70). Among patients diagnosed with SCN, 33.3% (n=8) showed glucose less than 40 mg/dL. Among patients with MNCPs, only 7.1% (n=5) showed glucose more than 40 ml/dL. The AUROC for glucose level in distinguishing between SCN and MNPCs was 0.866 (95% CI: 0.772–0.961, P <.01) with a cut-off of 46 mg/dL, demonstrating a sensitivity and specificity of 66.7% and 94%, respectively (Fig. 3).

Figure 3. (A) Boxplot of cystic glucose concentration in MNPCs and serous cystadenoma (B) Receiver operating characteristic curve with a cut-off of 46 mg/dL.

(A)



(B)

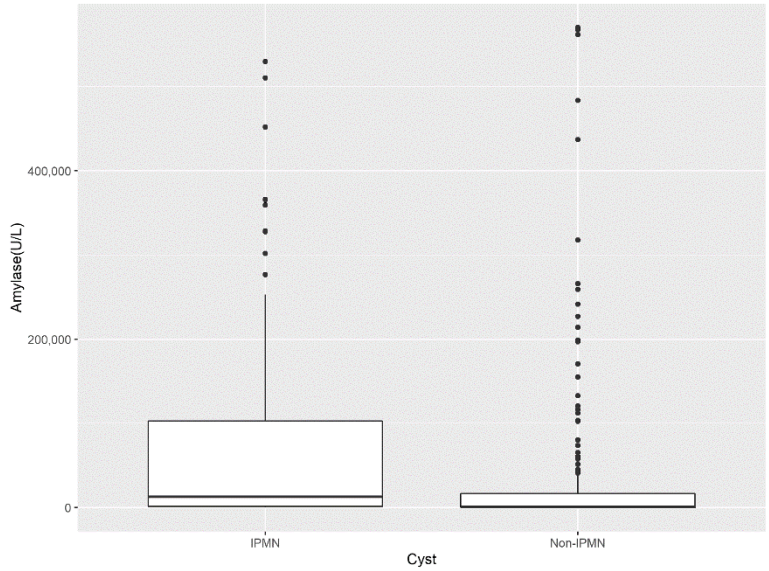


Cystic amylase for differentiating IPMN from non-IPMNs

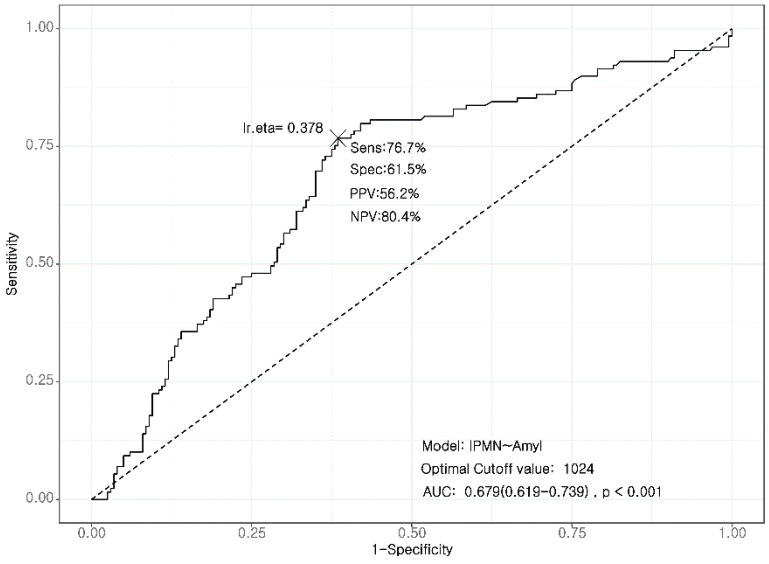
As IPMN is intraductal lesion, it can be assumed that IPMN could show high amylase level. Among the 352 patients, 329 patients (IPMN, n=129; non-IPMN, n=200) had cystic amylase results. Among IPMN patients, 23.3% of patients (n=30) showed amylase level less than 1000 IU/L. 17.1% of patients (n=22) had less than 2 times of serum upper normal level, and 10.9% (n=14) had less than serum upper normal level. The AUROC for amylase level in distinguishing IPMN from non-IPMN was 0.679 (95% CI: 0.619–0.739, P <.01) with a cut-off of 1024 IU/L, demonstrating sensitivity and specificity of 76.7% and 61.5%, respectively (Fig. 4).

Figure 4. (A) Boxplot of cystic amylase concentration in IPMNs and non-IPMNs (B) Receiver operating characteristic curve with a cut-off of 1024 IU/L.

(A)



(B)



Discussion

In this study, cystic CEA demonstrated a sensitivity of 91.3% and specificity of 75% with a cutoff level set at 8.8 ng/mL. Glucose or combining glucose with CEA did not show better diagnostic performance than CEA alone. TTNB offers an advantage over fluid analysis by providing an accurate diagnosis via tissue sampling with a high diagnostic yield over 80%.[8] However, for some patients with inadequate tissue acquisition, aspirated cystic fluid could enhance the diagnostic performance of TTNB. Our group initially achieved a diagnostic yield of 82%.[7] However, a meta-analysis reported a diagnostic yield of 69.5% (95% CI: 59.2–79.7) for EUS-TTNB.[9] For some patients with inadequate tissue acquisition, aspirated cystic fluid could enhance the diagnostic performance of TTNB. Moreover, TTNB when coupled with complete aspiration of the cyst, resulted in fewer adverse events (OR 0.56, 95% CI: 0.31–0.95; P = 0.02).[10] Therefore, utilizing the aspirated fluid can make the test safer and may also enhance its diagnostic value.

Fluids in cysts have been highlighted as a potential diagnostic tool because they are relatively protected matrices with high concentrations of secreted proteins, DNA, RNA, and metabolites related to tumor biology. Traditionally, fluid CEA has been evaluated; however, the results are disappointing when performed alone.[11] Previous studies on fluid analysis included a small number of patients, and the optimal cut-off level is controversial. Therefore, we aimed to reevaluate the role of fluid analysis.

Currently, American College of Gastroenterology guidelines recommend cyst fluid analysis for CEA and amylase, with limited evidence.[4] European guidelines suggest combining CEA with cytology, or mutations such as KRAS/GNAS.[3] They both cite 192 ng/mL as a cut-off level for MNPC differentiation. A recent meta-analysis showed pooled specificity of 88.6% (95% CI 85.9–90.9) and pooled sensitivity 60.4% (95% CI 57.7–62.9) across 15 studies.[12] However, real-world data showed suboptimal accuracy for differentiating MNPCs from non-MNPCs.[11] Some propose lower cut-offs. Gaddam et al. suggests 105 ng/mL for better performance with 70% sensitivity and 63% specificity.[11] Sharma et al. suggests 45 ng/mL as the most accurate marker to differentiate MCNs and NMCNs with 88.5% sensitivity and 96.8% specificity.[13] Oh et al. suggest 48.6 ng/mL as the most optimal cut-off level with 72.4% sensitivity and 94.7% specificity.[14] Our data also showed cystic CEA is clinically suboptimal

for differentiating MNPCs at 192 ng/mL with a sensitivity and specificity of 53.8% and 87.9%, respectively. The data suggested 8.8 ng/mL was a better cut-off level, with 91.3% sensitivity and 75% specificity. As our cutoff level was lower than that in other studies, it showed higher sensitivity and lower specificity. These differences could be due to different populations and heterogeneous indications.

Cystic glucose levels have been introduced as a diagnostic marker for differentiating MNPCs. Park et al. reported that glucose was significantly elevated in serous cystadenoma and used 66 mg/dL as the cut-off level, suggesting a novel fluid marker.[15] Carr et al. reported glucose as a better marker with a cut-off level <50 mg/dL.[16] Smith et al. reported that an cystic glucose level <25 mg/dL has better diagnostic performance than the traditionally reported cystic CEA level set at 192 ng/mL.[17] The AUROC was 0.96, with a sensitivity and specificity of 88.1% and 91.2%, respectively; however, with a small sample size (n = 93). There were no other cut-off levels of CEA for better performance. A meta-analysis of six studies found 91% pooled sensitivity and 85% pooled specificity of cystic fluid glucose in MNPC differentiation,[18] with cut-off levels ranging from 30 to 66 mg/dL. Even though the included population (n = 103) was much smaller than CEA, our data also suggested low glucose levels in MNPCs (median 2.0 mg/dL, range 2.0–74.0). The cutoff was 40 mg/dL, aligning with previous findings. Glucose testing is cost-effective and requires fewer resources.[18] However, its diagnostic role does not appear superior to that of cystic CEA.

One potential role of cystic glucose is to differentiate SCN from MNPC. We performed an additional subgroup analysis after excluding non-MNPCs (NET, pseudocysts, etc.) other than SCN. The AUROC increased from 0.742 to 0.866, with a cutoff of 46 mg/dL. Glucose may help differentiate SCN from MNPC in imaging studies when biopsy results are inconclusive.

The integration of CEA and glucose is important. Gorris et al. emphasized the significance of combined CEA and glucose testing in pancreatic cystic fluid, achieving the highest sensitivity (over 95%) for MNPCs with a lowered CEA cutoff ($\geq$20 ng/mL) and a 100% negative predictive value for glucose (cutoff: 50 mg/dL).[19] Our data showed that when the cystic fluid showed either CEA > 8.8 ng/mL or glucose <40 mg/dL, the sensitivity and negative predictive value reached 100%, but the specificity decreased to 51.5%. The AUC of the combination was lower than that of CEA alone. Despite the limitation imposed by our relatively modest sample size (n=103), using certain criteria—such as when CEA levels are

below 8.8 ng/mL and glucose levels are above 40 mg/dL—suggests a very lower chance of having MNPC, which could be a reason to avoid unnecessary surgery.

The roles of cystic CEA and glucose and their optimal cutoff levels have been discussed for several years; however, their cut-off levels have not been determined. The main issue with the current recommended CEA cutoff level of 192 ng/mL is its low sensitivity of approximately 60%. The pooled specificity of 88.6% and sensitivity of 60.4% was unsatisfactory. As previously mentioned, the optimal cut-off level of CEA ranged from 8.8 ng/mL to 192 ng/mL, and glucose ranged from 25 mg/dL to 66 mg/dL. Even though appropriate use of CEA or glucose may help differentiate MNPCs from non-MNPCs, these broad cut-off ranges can be confusing for clinicians, warranting cautious clinical application. Other markers, such as next-generation DNA analyses, should be developed for diagnosing MPCN and advanced neoplasia.[20]

The strength of our study is the large number of patients with pathological results via surgery or TTNB. As all laboratory examinations were performed at a single center, the credibility was high. However, this study had several limitations. First, there was selection bias occurred owing to the retrospective design, with some patients not undergoing cystic fluid examination owing to potential difficulties in collecting viscous cystic fluid using fine needles. Second, cystic glucose was collected from only 103 patients, possibly because glucose is a relatively novel marker for differentiating MNPCs. Third, viscosity or the presence of mucin upon cytological examination was not evaluated.

In conclusion, owing to the inconsistent cutoff values in different studies and sub-optimal diagnostic accuracy, the use of cystic CEA or glucose should serve a supplementary role. Research should focus on new diagnostic markers for cystic fluid to enhance diagnostic precision.

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국문요약

배경: 영상 검사만을 통해 췌장 낭성 병변(PCLs)을 정확하게 진단하는 것은 어려울 수 있다. 낭성 병변의 흡인액에서 암배아항원(CEA) 및 포도당을 측정하는 것은 점액성 낭성종양(MNPCs)과 비점액성 낭성종양(non-MNPC)간의 감별 진단에 도움이 될 수 있다. 본 연구에서는 PCLs 에 대한 치료 결정에 있어 낭성 병변의 흡인액의 진단적 역할을 평가하였다.

연구방법: 2006 년 1 월부터 2021 년 12 월까지 PCLs 에 대해 췌장 수술 전 또는 세침 바늘을 통한 조직검사 (through the needle biopsy, TTNB)를 통해 낭성 병변의 흡인액 검사를 받은 환자들을 대상으로 하였다. 자료의 수집과 분석은 후향적으로 수집되었다. PCLs 의 감별 진단을 위한 흡인액의 CEA 및 포도당의 진단적 가치를 분석하였다.

결과: 총 352 명의 환자가 분석에 포함되었다. 이 중 264 명은 MNPC 로 진단되었고, 88 명은 non-MNPC 로 진단되었다. MNPC 와 non-MNPC 를 구별하기 위한 CEA 수준의 ROC 곡선 아래 면적(AUROC)은 0.866 이었으며 (95% 신뢰 구간: 0.816-0.916, P <0.01), 8.8 ng/mL 의 기준값으로 감지되었다. 이는 각각 91.3%의 민감도와 75%의 특이도를 나타냈다. 가장 일반적으로 사용되는 192 ng/mL 의 기준값에서 AUROC 는 0.718 이었으며 (95% 신뢰 구간: 0.674-0.762, P <0.001), 민감도와 특이도는 각각 53.8%와 87.9%였다. 포도당 단독 또는 포도당 및/또는 CEA 를 결합하여 사용한 경우 CEA 만 사용한 것보다 더 나은 진단 성능을 보이지 않았다.

결론: 다양한 연구에서 서로 다른 기준값과 부적절한 진단 정확도로 인해, 흡인액의 CEA 또는 포도당의 사용은 보조적인 역할로 제한되어야 한다. 따라서 낭성 흡인액의 진단 정확도를 향상시키기 위해 새로운 진단 마커를 탐색하는 것이 중요하겠다.

중심단어: 췌장; 신생물; 암배아항원; 포도당