Intracystic Glucose and Carcinoembryonic Antigen in Differentiating Histologically Confirmed Pancreatic Mucinous Neoplastic Cysts

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INTRODUCTION: **Differentiating mucinous neoplastic pancreatic cysts (MNPC) from cysts without malignant potential can be challenging. Guidelines recommend using fluid carcinoembryonic antigen (CEA) to differentiate MNPC; however, its sensitivity and specificity vary widely. Intracystic glucose concentration has shown promise in differentiating MNPC, but data are limited to frozen specimens and cohorts of patients without histologic diagnoses. This study aimed to compare glucose and CEA concentrations in differentiating MNPC using fresh fluid obtained from cysts with confirmatory histologic diagnoses.**

METHODS: **This multicenter cohort study consisted of patients undergoing endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA) for pancreatic cysts during January 2013–May 2020. Patients were included if the cyst exhibited a histologic diagnosis and if both CEA and glucose were analyzed from fresh fluid. Receiver operating curve (ROC) characteristics were analyzed, and various diagnostic parameters were compared.**

RESULTS: **Ninety-three patients, of whom 59 presented with MNPC, met the eligibility criteria. The area under the receiver operating curve (AUROC) was 0.96 for glucose and 0.81 for CEA (difference 0.145, $P = 0.003$). A CEA concentration of ≥192 ng/mL had sensitivity of 62.7% and specificity of 88.2% in differentiating MNPC, whereas glucose concentration of ≤25 mg/dL had sensitivity and specificity of 88.1% and 91.2%, respectively.**

DISCUSSION: **Intracystic glucose is superior to CEA concentration for differentiating MNPC when analyzed from freshly obtained fluid of cysts with histologic diagnoses. The advantage of glucose is augmented by its low cost and ease of implementation, and therefore, its widespread adoption should come without barriers. Glucose has supplanted CEA as the best fluid biomarker in differentiating MNPC.**

Am J Gastroenterol 2022;117:478–485. https://doi.org/10.14309/ajg.0000000000001623

INTRODUCTION

The prevalence of pancreatic cystic lesions (PCLs) ranges from 2.4% to 19.6% and is increasing because of the widespread use of cross-sectional imaging (1,2). The definitive diagnosis of PCLs is important because it has implications on surveillance and treatment (3). Identifying PCLs with no malignant potential with a high degree of certainty reduces cost and may prevent unnecessary surgical resection. By contrast, diagnosing PCLs with malignant potential allows for appropriate imaging surveillance or surgical resection if worrisome features or early cancer is present. A common and important differentiation to make is whether a PCL represents a mucinous neoplastic pancreatic cyst (MNPC) or a non-MNPC. MNPCs, specifically intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, comprise most premalignant PCLs. Along with clinical history and radiological imaging, endoscopic ultrasound (EUS) fine needle aspiration (FNA) offers important information. Historically, the most common diagnostic tests of PCL fluid to differentiate MNPCs are carcinoembryonic antigen (CEA), amylase, and fluid cytology (4). Of these, CEA has demonstrated the highest accuracy in differentiating MNPCs from non-MNPCs (5,6). Although current guidelines recommend the use of CEA with a cutoff of ≥192 ng/mL to differentiate MNPCs, its sensitivity and specificity varies from 52% to 78% and from 63% to 91%, respectively (4,7). This has resulted in the study of many other diagnostic tests and tissue acquisition methods over the past 20 years; however, nothing has been adopted

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Received July 27, 2021; accepted December 29, 2021; published online December 31, 2021

as part of widespread clinical practice, mainly due to limitations in cost, availability, implementation, and clinical expertise.

Recently, data have shown that intracystic glucose concentration is lower in MNPC compared with non-MNPC, partly due to the glucose metabolism of active neoplastic cells (8,9). Several studies have demonstrated the superiority of low glucose concentrations to high CEA concentrations in differentiating MNPC; however, these studies have been limited in 3 aspects: single-center designs, the use of frozen fluid, and the lack of histologic confirmation as the gold standard (10–14). The aim of this multicenter study was to assess the comparative diagnostic yield of intracystic glucose and CEA concentrations in differentiating MNPC and non-MNPC from fresh fluid samples of cysts with definitive histology.

METHODS

Study design and patient selection

This was a multicenter, international, retrospective cohort study of patients from 3 centers: University Hospitals, Cleveland, OH; Cleveland Clinic Foundation, Cleveland, OH; and Hospital General Universitario de Alicante, Alicante. Spain. Consecutive patients undergoing EUS-guided FNA in the diagnostic workup of PCL from January 2013 to May 2020 were assessed for eligibility. Patients were eligible if (i) fresh fluid from a discrete PCL was sampled and tested for CEA and glucose concentration and (ii) the sampled cyst exhibited a concomitant or subsequent confirmed histologic diagnosis. Exclusion criteria were applied to determine eligible subjects in sequential order as follows: lack of histology, glucose present and CEA absent, glucose absent and CEA present, and neither glucose nor CEA present. Twenty patients have been described in a previous report (13). All 3 sites received Institutional Review Board approval.

Procedural techniques

All EUS procedures were performed with curvilinear array echoendoscopes (GF-UCT180 and GF-UC140P-AL5, Olympus Corporation of The Americas, Center Valley, PA). PCLs were sampled with 22-gauge or 25-gauge needles (EZ Shot 3 Plus, Olympus Corp, Center Valley, PA; SharkCore, Medtronic, Fridley, MN; Expect Slimline, Boston Scientific, Marlborough, MA). For patients with multiple cysts sampled, only the largest was included for analysis. Sampled fluid was placed into a dry sterile container and transported to the on-site chemistry laboratory. Glucose and amylase testing were performed using automated clinical chemistry laboratory analyzers (cobas c 702, Roche Diagnostics, Indianapolis, IN; AU5800, Beckman Coulter, Brea, CA). All CEA testing was performed using electrochemiluminescent immunoassay (Roche Diagnostics). Histologic confirmation was performed on tissue obtained by 1 of 3 methods: through-the-needle microforceps (Moray Micro Forceps, STERIS Endoscopy, Mentor, OH) biopsy of the cyst wall, fine-needle biopsy of the cyst wall after aspiration, or surgical resection.

Data collection

Patient demographics at the time of EUS were recorded. Patients were assessed for the prevalence of diabetes at the time of EUS by either a documented diagnosis of diabetes or the concomitant use of hypoglycemic agents. Procedure and imaging reports were reviewed for various cyst characteristics, including size, location (head, uncinate process, neck, body, and tail), morphology, worrisome features or high-risk stigmata (15), and pancreatic duct diameter. Fasting plasma glucose level, if checked at the time of EUS, was recorded. Laboratory and pathology reports were reviewed for CEA and glucose concentrations and histologic diagnoses. Two sites used minimum reportable thresholds for glucose concentration: site 1 reported values lower than 10 mg/dL as "<10 mg/dL," and site 3 reported values less than 3 mg/dL as "<3 mg/dL" In these circumstances, the highest value below the reporting threshold was recorded as the discrete data point (e.g. 9 mg/dL for reported values of <10 mg/dL). In cases where 2 methods resulted in a congruent diagnosis (e.g. fine-needle biopsy followed by surgical resection), the earlier chronological method was recorded.

Outcomes

The primary outcomes were diagnostic parameters differentiating MNPC from non-MNPC, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy, and area under the receiver operating curve (AUROC). The AUROC curves were used to obtain the threshold values for glucose in which to compare these diagnostic parameters. Because of historical significance, a CEA value threshold of 192 ng/mL was used (16).

Statistical analysis

Descriptive statistics were used to report the mean values and SD for normally distributed data and the median with range for skewed data. Univariate analyses were performed to compare patient characteristics using the Fisher exact or the Pearson χ^2 tests, where appropriate. Receiver operating curve (ROC) characteristics were performed to assess diagnostic yield of glucose and CEA concentration, and the curves were compared using the DeLong method (17). ROC characteristics were used to assess the

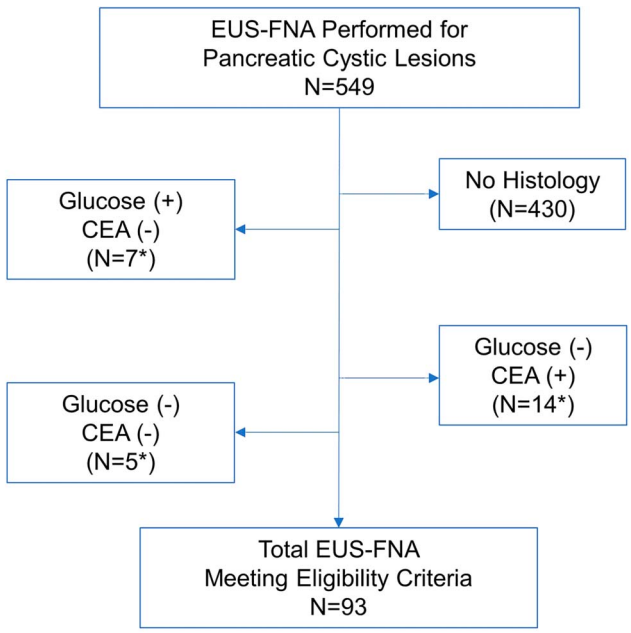

Figure 1. Flowchart outlining study subject eligibility criteria selection. EUS-FNA, endoscopic ultrasound with fine-needle aspiration; CEA, carcinoembryonic antigen.

diagnostic accuracy at various levels of glucose concentration to identify the optimal thresholds for the differentiation of MNPC. Sensitivity, specificity, NPV, PPV, and diagnostic accuracy were calculated for glucose at 2 thresholds (based on the ROC coordinates), CEA levels ≥192 ng/mL in isolate, and low glucose and high CEA in combination. To assess for variance in testing across institutions, CEA and amylase levels for mucinous cysts were compared across the 3 sites using the nonparametric Kruskal-Wallis test. This comparison was not performed for glucose because several values were reported as below a reporting threshold (e.g., <10 mg/dL) and not as integers. Fasting plasma glucose was compared across histologic subtypes using the Kruskal-Wallis test. A 2-sided *P* value of 0.05 was considered significant. All analyses were performed with SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, NY) and MedCalc for Windows, version 19.7 (MedCalc Software, Ostend, Belgium). All authors had access to the aggregate study data and approved the final manuscript.

RESULTS

Patient cohort characteristics

Ninety-three patients, 59 with MNPC and 34 with non-MNPC, met eligibility criteria (Figure 1). There were 26 instances in which both CEA and glucose were not analyzed because of insufficient fluid volume and/or the viscosity of the fluid. Patient demographics and clinical features of the various PCLs are summarized in Table 1. The mean age was 67 years ± 9.8 years, and 54.8% were female individuals. Sixty patients had 1 PCL (64.5%). The breakdown of anatomic location of PCLs is presented in Table 1. The 3 most common anatomical sites were head (n = 27, 29.0%), body (n = 30, 32.3%), and tail (n = 25, 26.8%). There were no significant differences between patients in the MNPC and non-MNPC cohorts regarding age, sex, PCL size or location, pancreatic duct diameter, or volume of PCL fluid acquired (Table 1). Details regarding histology and methods of tissue acquisition are listed in Table 2. The number of diabetic patients and the fasting plasma glucose levels per histologic type are presented in Table 3. A total of 65 patients had a fasting plasma glucose level checked at the time of EUS-FNA.

Performance of glucose and CEA in differentiating MNPC

For MNPC, the median glucose concentration was 4 mg/dL (interquartile range [IQR] 2–9) and the median CEA concentration was 397 ng/mL (IQR 56.9–1,892.6) (Table 4). For non-MNPC, the median glucose concentration was 92.5 mg/dL (IQR 47.8–115.5) and the median CEA concentration was 7.2 ng/mL (IQR 1.3–70.9) (Table 4). Three non-MNPC had glucose concentrations ≤25 mg/dL: 1 simple mucinous cyst (histology confirmed on surgical resection) (18–21), 1 gastrointestinal stromal tumor with a large cystic component, and 1 pseudocyst. The AUROC for glucose was significantly higher when compared with that for CEA in differentiating MNPC (0.96 vs 0.81, difference 0.145, $P = 0.003$) (Figure 2). A CEA concentration ≥192 ng/mL had sensitivity of 62.7% and specificity of 88.2%; PPV of 90.2%, NPV of 57.7%, and diagnostic accuracy of 72.04% (95% confidence interval 61.78%–80.86%) in differentiating MNPC (Table 5). By contrast, glucose concentrations ≤25 mg/dL had sensitivity of 88.1% and specificity of 91.2%; PPV of 94.6%, NPV of 81.6%, and diagnostic accuracy of 89.3% (95% confidence interval 81.11%–94.72%) (Table 5). Glucose concentrations ≤40 mg/dL had sensitivity of 94.9%, specificity of 82.4%, and PPV, NPV, and diagnostic accuracies, each of 90.3% (Table 5).

When combining low glucose and high CEA concentrations in differentiating MNPC, the specificity and PPV increased, whereas sensitivity, NPV, and overall diagnostic accuracy fell in comparison with glucose concentration alone (Table 5).

Table 1. Baseline characteristics of patients with mucinous neoplastic pancreatic cysts (MNPC) and non-MNPC

Characteristic	Mucinous neoplastic pancreatic cyst (MNPC) (N = 59)	Non-MNPC (N = 34)	*P* value
Age (mean age in yr ±SD)	66.6 ± 9.9	62.3 ± 14.1	0.09
Female sex (%)	33 (55.9)	18 (52.9)	0.78
PCL maximum diameter (mean, mm ± SD)	37.1 ± 22.4	40.3 ± 24.8	0.54
PCL anatomic location (%)			0.21
Head	19 (32.2)	8 (23.5)	
Neck	8 (8.7)	8 (13.6)	
Body	17 (28.8)	13 (38.2)	
Tail	13 (22.0)	12 (35.3)	
Uncinate process	1 (3.4%)	2 (2.9)	
Septations			0.17
Unilocular	27	20	
Single septation (bilobed)	2	3	
Multicystic	30	11	
Maximum pancreatic duct diameter (mean, mm ± SD)	4.4 ± 4.4	4.7 ± 13.6	0.90
Volume of PCL fluid aspirated (mean, mL ± SD)	4.3 ± 6.8	6.2 ± 9.5	0.33

PCL, pancreatic cystic lesion.

Table 2. Methods of tissue acquisition for histologic diagnosis

Histologic diagnosis	Method of tissue acquisition for histologic diagnosis			Total
	Through-the-needle forceps biopsy	Fine-needle biopsy of cyst wall	Surgical resection	
Total	16	32	45	93
Main duct IPMN	0	2	8	10
Branch duct IPMN	7	2	7	16
Mixed IPMN	0	0	5	5
IPMN with invasive cancer	0	3	5	8
Mucinous cystic neoplasm	1	4	8	13
Mucinous cystic neoplasm with invasive cancer	0	6	1	7
Pseudocyst	0	4	3	7
Serous cystadenoma	3	3	4	10
Cystic neuroendocrine tumor	4	4	1	9
Other	1	4	3	8[a]

IPMN, intraductal papillary mucinous neoplasm.
[a]Other includes simple mucinous cyst (1), gastrointestinal stromal tumor, spindle type, with cystic component (1), undifferentiated carcinoma with osteoclast-like giant cells (1), paraduodenal wall cyst (2), benign cyst and fibroadipose tissue (1), cystic lymphangioma (1), and Schwannoma (1).

Testing variance by site

Tests for normality of distribution demonstrated skewed distribution for glucose, amylase, and CEA concentrations. There were no significant variances in results for CEA concentration in MNPC (Kruskall-Wallis H = 4.3, $P = 0.12$) or in non-MNPC (Kruskall-Wallis H 2.5, $P = 0.29$) across the 3 study sites. There was no significant difference in amylase levels across the 3 sites (Kruskall-Wallis H 2.5, $P = 0.28$). There was a slight, but significant variance in glucose concentrations for non-MNPC across the 3 sites (Kruskall-Wallis H 6.2, $P = 0.044$).

DISCUSSION

The role of PCL fluid analytics in diagnosing MNPC has been of interest for over 2 decades, and in fact, early studies predate the widespread availability of EUS (5,6,22–25). To date, CEA is the most widely studied component of pancreatic cyst fluid. Studies during the early phases of EUS-FNA showed enthusiasm for the potential of CEA concentration (26,27). A landmark study by Brugge et al. (16) in 2004 lauded CEA as the most accurate test in the diagnosis of MNPC, with optimization demonstrated at ≥192 ng/mL. The position of CEA as the gold standard has remained relatively unchallenged for more than 20 years despite studies repeatedly identifying its inadequacies (28–30). Many glycoproteins, biomarkers, and molecular assays have been studied, but none have become commonplace in standard clinical practice for myriad reasons (31–42).

The role of glucose concentration in diagnosing MNPC was first identified by Park et al. (8), and since then, several studies have investigated the accuracy of glucose when compared with CEA (10–14). These studies have been limited by several factors, including lack of histologic confirmation (12,13), the use of banked frozen fluid (10,11,14), and lack of multicenter validation (10–14). Our study aimed to overcome these limitations by performing a multicenter analysis of fresh cyst fluid from histologically confirmed MNPC. The results of this study show that when comparing glucose thresholds of ≤25 and ≤40 mg/dL with a CEA threshold of ≥192 ng/mL, glucose has superior sensitivity, specificity, and accuracy in differentiating MNPC. Furthermore,

Table 3. Fasting plasma glucose (at the time of EUS) and the number of diabetic patients by histologic type

Histologic diagnosis	Fasting plasma glucose (mg/dL) (median, range)	*P* value	Diabetic patients N (%)	*P* value
Main duct IPMN	115 (106–147)	0.49	5 (50%)	0.063
Branch duct IPMN	102.5 (74–147)		3 (18.8%)	
Mixed IPMN	93.5 (84–223)		3 (60%)	
IPMN with invasive cancer	116 (91–188)		1 (12.5%)	
Mucinous cystic neoplasm	109.5 (88–162)		4 (30.8%)	
Mucinous cystic neoplasm with invasive cancer	100 (97–184)		7 (100%)	
Pseudocyst	113 (88–187)		5 (71.4%	
Serous cystadenoma	94 (85–143)		4 (40%)	
Cystic neuroendocrine tumor	135 (83–437)		5 (55.6%)	
Other	99.5 (94–132)		2 (25%)	

EUS, endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm.

Table 4. Glucose, CEA, and amylase concentration stratified by histologic type (median, range)

Histologic diagnosis	Fluid diagnostic test		
	Glucose (mg/dL)	CEA (ng/mL)	Amylase (U/L)
Main duct IPMN	2 (2–9)	568.5 (2.2–3,604)	8,356 (3–588,224)
Branch duct IPMN	4 (0–112)	58.9 (1.4–1,297)	5,113.5 (465–558,580)
Mixed IPMN	3 (2–24)	201.8 (4.3–298.9)	47,402.5 (275–202,909)
IPMN with invasive cancer	6.5 (1–86)	604.4 (22–3,872)	902 (2–93,300)
Mucinous cystic neoplasm	9 (2–34)	205 (56–10,001)	706 (3–86,700)
Mucinous cystic neoplasm with invasive cancer	10 (9–70)	10,000 (4,714–65,170)	35.5 (9–139)
Pseudocyst	71 (15–150)	108.1 (2.9–416)	71,376.7 (6,001–204,102)
Serous cystadenoma	86 (29–173)	1.8 (0.1–687.9)	124 (9–71,800)
Cystic neuroendocrine tumor	120 (92–446)	4.9 (0.7–26.7)	114 (9–150,000)
Other	37 (11–111)	11.3 (0.2–10,001)	88 (20–6,001)

CEA, carcinoembryonic antigen; IPMN, intraductal papillary mucinous neoplasm.

whereas the concomitant presence of low glucose and high CEA concentrations improves specificity and PPV in differentiating MNPC, this comes at the expense of lower sensitivity, NPV, and diagnostic accuracy. In other words, glucose concentration as a stand-alone test is superior to CEA alone or glucose and CEA in differentiating MNPC.

Throughout the past 25 years, 2 research aims have remained paramount: the ability to differentiate MNPC from non-MNPC and the ability to assess the presence and/or future risk of dysplasia and malignancy. In differentiating MNPC from non-MNPC, glucose has demonstrated clear superiority in direct comparison with CEA concentration and indirectly with fluid cytology (10–14,43). Whereas other glycoproteins and next-generation sequencing have shown good accuracy in differentiating MNPC, these tests are hindered by their availability and cost (31,32,34,36) and are primarily used in assessing malignancy risk/histologic grade, something which neither CEA nor glucose concentrations are capable of. By contrast, testing body fluid glucose concentration is inexpensive and has been commercially available since 1908 (44).

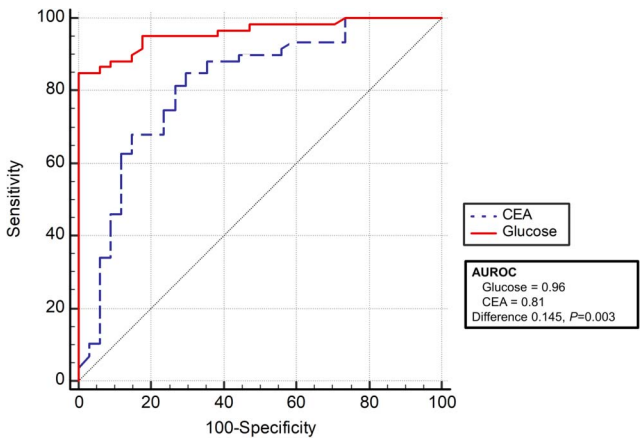

Figure 2. Receiver operating curves for glucose and CEA concentration from fresh cyst fluid in the differentiation of MNPC. AUROC, area under the receiver operating curve; CEA, carcinoembryonic antigen; MNPC, mucinous neoplastic pancreatic cyst.

Recently, 2 newer accessories have added to the diagnostic armamentarium of PCLs. Through-the-needle forceps biopsy (TTNFB) using a microforceps and needle-based confocal laser endomicroscopy (nCLE) are both accurate in differentiating MNPC. Unlike CEA and glucose, these can also provide information on histologic grade and the presence of invasive cancer (45,46). Although studies have shown better accuracy with TTNFB and nCLE in differentiating MNPC compared with CEA and fluid cytology, these techniques have never been directly compared with glucose concentration (45,47,48). Moreover, the routine use of these accessories in differentiating MNPC among all-comers has not been compared with glucose in a cost-effectiveness analysis. Owing to the device and equipment costs of TTNB and nCLE (49), it is intuitive that glucose is the most cost-effective test for differentiating MNPC in routine clinical care, likely by a substantial margin. Furthermore, the use of TTNFB and nCLE have been associated with higher rates of procedure-related adverse events compared with standard FNA, specifically bleeding and pancreatitis (47,50–52). A recent systematic review of studies examining TTNFB in 423 patients identified a pooled AE rate of 10.1% (51), but these AE rates are likely attenuated for providers that perform a high volume of these procedures (45).

There are several strengths of this study. First, our study analyzed fresh fluid from PCLs. Previous studies analyzing the diagnostic yield of glucose compared with that of CEA have performed so using frozen PCL fluid (10,11,14). Data from human serum samples suggest that there is a mean 10% degradation in serum CEA concentration after 10 months of frozen storage (53). Although long-term frozen storage has not been observed to negatively affect glucose concentration (54), studies comparing potentially degraded CEA to glucose using frozen PCL fluid may be inferior to testing fresh fluid. Second, our study included PCLs only with confirmed histology, improving on previous data analyzing PCL glucose concentration from fresh samples, for which histologic confirmation was only available in a minority of subjects (13). Third, whereas all testing was performed locally at each study site, the same method of CEA testing, electrochemiluminescent immunoassay, was used throughout the study, thereby mitigating confounding related to methodologic variance. Fourth, although

Table 5. Diagnostic test parameters of glucose and CEA concentrations in isolate and combination for differentiating MNPC (percentage with 95% CI)

	Cyst fluid test result			
Statistic	Glucose ≤25 mg/dL	Glucose ≤40 mg/dL	CEA ≥192 ng/mL	Glucose ≤40 mg/dL and CEA ≥192 ng/mL
Sensitivity	88.1% (77.1%–95.1%)	94.9% (85.9%–98.9%)	62.7% (49.2%–74.9%)	59.3% (45.8%–71.9%)
Specificity	91.2% (76.3%–98.1%)	82.4% (65.5%–93.2%)	88.2% (72.6%–96.7%)	97.1% (84.7%–99.9%)
Positive predictive value	94.6% (85.4%–98.1%)	90.3% (81.8%–95.1%)	90.2% (78.3%–95.9%)	97.22% (83.4%–99.6%)
Negative predictive value	81.6% (68.7%–89.9%)	90.3% (75.4%–96.6%)	57.7% (48.9%–66.0%)	57.9% (50.1%–65.3%)
Diagnostic accuracy	89.3% (81.1%–94.7%)	90.3% (82.4%–95.5%)	72.0% (61.8%–80.9%)	73.1% (62.9%–81.8%)

CEA, carcinoembryonic antigen; CI, confidence interval; MNPC, mucinous neoplastic pancreatic cyst.

this study is retrospective, the 3 sites were carefully selected because there was no meaningful variability in clinical practice protocols regarding EUS-FNA technique or PCL fluid testing. Therefore, the multicenter and international makeup of this study adds significantly to the generalizability of its results and improves on the single-center studies that precede it (10–14). Finally, we also demonstrated that there was no significant difference in the number of diabetic patients or in fasting plasma glucose level across any of the histologic subtypes, thereby reducing the potential of confounding cyst fluid glucose concentrations in diabetic patients.

There are also some limitations to acknowledge. First, glucose concentration was tested on different chemistry analyzers, and although each model has established data on its analytical performance (55–57), specimens were not centrally validated. Although the Kruskal-Wallis test did demonstrate mild variance in glucose results for non-MNPC, 2 rare lesions—a simple mucinous cyst and a cystic malignant gastrointestinal stromal tumor from sites 2 and 3—may have contributed to this variance. Second, because this was a retrospective study, there was not a uniform protocol for specimen acquisition and collection, although as mentioned earlier, the standard protocols of clinical practice contained little variation among the 3 sites. Third, although more than 10 different cyst subtypes are represented in this study, 63.4% of PCLs were MNPC. It is possible that a more balanced cohort of PCL may have altered the observed diagnostic accuracy of CEA and glucose, though likely not significantly. Finally, this study included 93 patients over a 7-year period. One may argue that this raises concern for selection bias. In the early years of this study, the authors were the only providers at their respective institutions sending PCL fluid for glucose concentration. Furthermore, confirmation of PCL histology by EUS has only become more achievable recently with the advent of TTNB and FNB needles, therefore making the overall proportion of PCLs that meet eligibility criteria for this study rather small. Because this study relies on histologic confirmation as the gold standard, the number of patients excluded was high. Furthermore, in aspirates where only 1 or neither of glucose nor CEA was analyzed, this was the result of insufficient fluid volume or viscosity and not because of physician bias. Finally, the glucose concentration thresholds of ≤25 and ≤40 mg/dL were chosen based on their superior performance to other levels on ROC analysis. Because of the relatively small sample size, we were unable to test these in a validation cohort, something which would have required additional subjects to be enrolled from other institutions.

In conclusion, glucose concentration in PCL fluid is highly accurate in differentiating MNPCs from non-MNPCs and may be superior to CEA concentration. Because of its ease of implementation, low cost, and lack of incremental increases in adverse events, glucose concentration should be part of the standard of care in differentiating MNPC, and moreover, it seems to be superior to CEA for this important distinction. Future studies evaluating the utility of TTNFB, nCLE, and other novel biomarkers and diagnostic tests for differentiating MNPC must be performed comparatively with routine testing that includes PCL fluid glucose concentration to be considered valid.

ACKNOWLEDGEMENTS

This study was selected for the ASGE Presidential Plenary Session at Digestive Disease Week 2021. Research efforts of Dr. Smith are supported partly by the Clement J. Zablocki VA Medical Center.

CONFLICTS OF INTEREST

Guarantor of article: Zachary L. Smith, DO.

Specific author contributions: Conception & Design: Z.L.S.; data collection: all authors; aggregate data assembly: Z.L.S. and S.S.; analysis and interpretation of the data: Z.L.S.; drafting the article: Z.L.S. and S.S.; critical revision of the article for important intellectual content: all authors. All authors approved the final version.

Financial support: None to report.

Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

✓ The differentiation of mucinous pancreatic cystic lesions (PCLs) can be challenging, and historically, this has relied on carcinoembryonic antigen (CEA), an imperfect test. Glucose concentration has shown promise as a more accurate alternative.

WHAT IS NEW HERE

✓ In lesions with definitive histology, glucose is far superior in sensitivity, specificity, and accuracy compared with CEA in differentiating mucinous PCLs and at little incremental cost. Endosonographers can greatly improve diagnostic accuracy for mucinous PCLs by implementing an inexpensive and widely available test.

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