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Pancreatic cyst fluid interleukin-1 beta (IL-1β) level in predicting the risk of malignancy in pancreatic cysts

Tarek A. Abdellah[1], Sayed M. Shalaby[1], Amira A. Salem[1], Tarek M. Yousef[1], Shereen A. Saleh[1], Hussein H. Okasha[2], Mariam S. Zaghloul[3] and Mohamed A. El-Nady[2]

[1]Department of Internal Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[2]Department of Internal Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt.

[3]Department of Hepatology, Gastroenterology & Infectious Diseases, Faculty of Medicine, Kafrelsheikh University, Kafrelsheikh, Egypt.

Corresponding author: Tarek A. Abdellah, Department of Internal Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
Email: taae1990@gmail.com

Abstract

Pancreatic cystic lesions (PCLs) may be accidentally discovered in up to 13.5% of cases. These PCLs are of multiple types, including mucinous cysts (intra-ductal papillary mucinous neoplasms [IPMN] and mucinous cystic neoplasms [MCN]) that have a risk of malignant transformation. The difficulty in differentiation between the various PCLs and their unpredictable risk of malignant transformation makes their management difficult. The new diagnostic tools of PCLs often include endoscopic ultrasound guided fine needle aspiration (EUS-FNA) for pancreatic cyst fluid analysis. This study aimed to determine if cystic fluid IL-1β can predict the risk of malignancy and the degrees of dysplasia of pancreatic cysts. The study included 50 PCL patients. They were subjected to radiological, biochemical, serological, and histopathological examinations. Pancreatic cyst fluid IL-1β was analyzed using an ELISA. Our data indicated that cyst fluid IL-1 β can differentiate between benign and malignant cysts at cut-off value >150 pg/ml; with sensitivity and specificity of 84.00% and 56.00% respectively. Also, cyst fluid IL-1 β can differentiate between mucinous and non- mucinous pancreatic cysts at cut-off value >150 pg/ml; with a sensitivity and specificity of 83.33% and 53.78%, respectively. However, cyst fluid IL-1 β cannot differentiate between degrees of dysplasia of IPMN. In conclusion, our study suggested that pancreatic cyst fluid IL-1β can differentiate between mucinous and non-mucinous pancreatic cysts and between benign and malignant pancreatic cysts.

Keywords: intra-ductal papillary mucinous neoplasm, pancreatic cyst, interleukin-1β, EUS fine needle aspiration.

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Introduction

The diagnostics of pancreatic cystic lesions (PCLs) is increasing. This is due to an increased use of high quality cross-sectional abdominal radiology.[1] PCLs represent multiple types of lesions including inflammatory, congenital,

and neoplastic cysts.[2] The World Health Organization (WHO) classifies PCLs either as has the risk of malignancy or as benign lesions. Intra-ductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), solid pseudopapillary neoplasms (SPN), and serous cystic neoplasms (SCN) are classified in the malignant list. IPMN and MCN are called mucinous cysts and both with SPN have a risk of malignant transformation.[3] SCN is considered benign cystic lesions,[4] and along with pseudo-cysts, retention cysts and lympho-epithelial cysts have no risk of malignant transformation making surgical excision and follow-up needless.[5] Guidelines should be recommended to assist in the treatment of pancreatic cystic lesions, which include surgical excision and follow-up strategy.[6] These recommendations depend on an accurate diagnosis of cyst type and diagnosis of the presence or absence of malignancy.[7] While greatly increasing the diagnosis of pancreatic cysts, cross-sectional imaging was found to be imperfect for the diagnosis of pancreatic cystic lesions with an accuracy of nearly 61% to distinguish between mucinous, non-mucinous cysts, and diagnosis of malignant PCLs.[8] Endoscopic ultrasound (EUS) is good for high-quality resolution of the pancreas; However, EUS diagnosis alone has an accuracy of 50-73% to distinguish between mucinous and non-mucinous cysts.[9] The current diagnostic tools of PCLs also include EUS guided fine needle aspiration (FNA) for cyst fluid analysis.[9]

Cell-mediated and humoral immune responses have been implicated in many tumors, as pancreatic adenocarcinoma.[10] Also, cytokine markers of the Th1 and Th2 immune response have been shown to differentiate chronic pancreatitis from pancreatic cancer or normal pancreatic tissue in both serum and pancreatic cystic fluid analysis.[10] We thought that dysplastic changes in PCLs initiate pro-inflammatory or immunogenic microenvironment that could be analyzed in the pancreatic cyst fluid sample and allow for the diagnosis of carcinoma or high-grade dysplasia before surgery. Consequently, our goal in this research was to evaluate the role of pancreatic cystic fluid IL-1B level in different types of pancreatic cysts, and its correlation with dysplastic changes.

Subjects and Methods

Ethical consideration

The study protocol was reviewed and approved by the Research Faculty of Medicine Ain Shams University (FMASU, MD 331/2018). An informed consent was obtained from each participant before included in the study.

Between January 2018 and November 2020, 50 PCL patients underwent EUS-FNA for cyst fluid analysis at the endoscopy unit of the Internal Medicine Department. Patients were with mean age 55.38 ± 7.98 years (range 35 – 68years). They were 25 male and 25 female patients.

All patients were subjected to full clinical examination and detailed history was taken. The patients were studied serologically for serum amylase and CA19-9 tuner marker using enzyme linked immune-sorbent assay (ELISA) kits as reported by Snozek et al., 2009.[4]

Radiological studies

All patients were submitted to computed topography (CT) pelvic-abdominal with contrast and/or abdominal magnetic resonance imaging (MRI) to describe the features of each pancreatic cyst (the presence of a mural nodule or solid component either within the cyst or in the pancreatic parenchyma, dilation of the main pancreatic of >5 mm, a focal dilation of the pancreatic duct concerning for main duct intraductal papillary mucinous neoplasms (IPMN) or an obstructing lesion, mucin producing cysts measuring ≥3 cm in diameter).

Interventional Studies

These included EUS performed using a Pentax linear array scope (EG3870UTK-Pentax, Japan) connected to a Hitachi Avius ultrasound machine (Hitachi Arietta, Tokyo). FNA was done by 22- gauge (Echo Tip, Cook Medical, IN, USA).

The final diagnosis was established according to the histopathological diagnosis of the resected specimens in patients who underwent surgery or malignant EUS-FNA aspirate and long-term clinical follow-up (at least for six months) with no change in size or development of metastasis.

Correlative studies, on cyst fluid carcinoembryonic antigen (CEA), were assessed by ELISA kit (Rattus norveggicus, SEA150Ra, cloud-clone, China), according to the manufacturer's instructions (threshold value 0.118ng /ml). Cyst fluid interleukin 1beta (IL-1 β) and FNA cytology were performed on these cyst fluid samples.

Aliquots of cyst fluid were stored at −20 °C and subsequently thawed on ice for biomarker testing. Demographics and clinical data were collected through review of electronic medical records.

Biomarker Measurement

Pancreatic cyst fluid IL-1β was analyzed using a commercial ELISA kit (Cat DLB-50; R&D, Minneapolis, Minn and RPN222; GE Healthcare Life Sciences, Pittsburgh, Pennsylvania, USA), according to the manufacturer's instructions (threshold value of IL-1β (>50 pg /mL).

Statistical analysis

Collected data were revised, coded, and entered in a computer using the Statistical Package for Social Science (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, New York: IBM Corp.). The quantitative data with parametric distribution have been presented as mean, standard deviations, and ranges while with non-parametric distribution have been presented as median with inter-quartile range (IQR). Also, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using Chi-square test and/or Fisher exact test when the expected count in any cell was found less than 5. The comparison between two independent groups regarding quantitative data with parametric distribution was done by using an independent t-test, while with non-parametric distribution was done by using Mann-Whitney test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters. The receiver operating characteristic (ROC) curve was used to assess the best cut-off point with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). Univariate and multivariate logistic regression analysis was used to assess the predictors of malignancy and mucinous cysts with its odds ratio (OR) and 95% confidence interval (CI). The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, *P* value of < 0.05 was considered significant.

Results

A total of 50 patients were included in this study (25 females, 25 males), their mean age was 55.38 ± 7.98. The majority of PCLs were located in the body (60%), while 56% in the head, and 24% in the tail of the pancreas. Most of IPMNs were found in the head (92.3%) (Table 1).

Table 1. Demographics and cysts characteristics of the 50 studied patients.

Studied parameter	Value
Age	
Mean ± SD	55.38 ± 7.98
Range	35 – 68
Sex	
Female	25 (50.0%)
Male	25 (50.0%)
Radiological findings (CT &/ MRI, EUS) site of cyst	
Pancreatic head	28 (56.0%)
Pancreatic neck	4 (8.0%)
Pancreatic body	30 (60.0%)
Pancreatic tail	12 (24.0%)
Size of cyst	
Mean ± SD	66.10 ± 29.52
Range	10 – 162

N.B: the lesion may include more than one anatomical region. CT: computed topography; MRI: magnetic resonance imaging; EUS: endoscopic ultrasound.

Table 2 shows the classification of pancreatic cysts according to cytopathology and final outcomes (benign or malignant). There was a

statistically significant correlation between IL-1β and C.F CEA (*P*=0.026). And there was a significant correlation between IL-1β and patient's age (*P*=0.002) (Table 3).

Table 2. Classification of pancreatic cysts in the 50 studies subjects according to cytopathology and final outcomes.

Parameter	Pancreatic cyst classification	No. (%)
Pancreatic cyst cytopathology	Intraductal papillary mucinoius neoplasm (IPMN)	12 (24.0%)
	Pancreatic pseudocyst	15 (30.0%)
	Mucinous cystic neoplasm	11 (22.0%)
	Serous cystadenoma	7 (14.0%)
	Cystic lymphangioma	1 (2.0%)
	Duplication cyst with multiple pancreatic retention cysts	1 (2.0%)
	Mucinous cystadencarcinoma	1 (2.0%)
	Pancreatic adenocarcinoma	1 (2.0%)
	Necrotizing pancreatitis with walled-off pancreatic necrosis (WOPN)	1 (2.0%)
Outcome	Benign	25 (50.0%)
	Malignant	25 (50.0%)
Mucin stain	Negative	26 (52.0%)
	Positive	24 (48.0%)

Table 3. Correlation between the cystic fluid CEA and IL-1B and other tested variables.

	C.f. CEA		C. f IL1β	
	r	*P*-value	r	*P*-value
C.f. CEA ng/ml	–	–	0.314*	0.026
C.f IL-1β pg/ml	0.314*	0.026	–	–
Age	0.255	NS	0.422**	0.002
Size of cyst mm	-0.075	NS	-0.273	NS
C.f. amylase u/l	0.015	NS	-0.042	NS

C. f. CEA (cystic fluid carcinoembryonic antigen). C. f IL-1β (cystic fluid interleukin 1 beta). *P* > 0.05 is not significant (NS).

The cutoff value of IL-1β in differentiating between benign and malignant pancreatic cysts was >150 pg/ml, with a sensitivity and specificity of 84% and 56%, respectively. The cutoff value of CEA in differentiating between benign and malignant pancreatic cysts was >61 ng/ml, with a sensitivity and specificity of 100% and 96%, respectively (Figure 1).

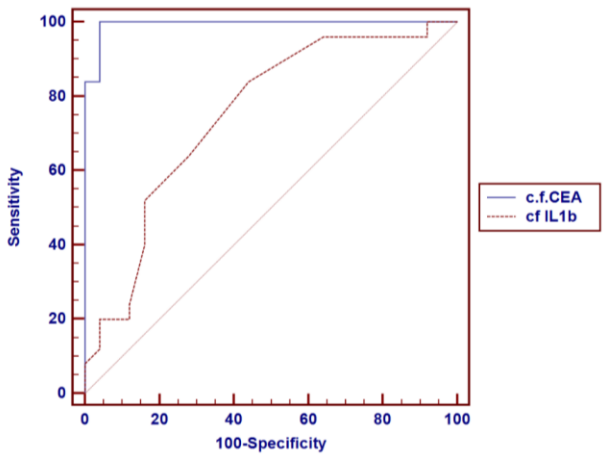

Figure 1. ROC curve analysis of IL-1β and CEA for differentiation between benign and malignant pancreatic cysts. C.F CEA (cystic fluid carcinoembryonic antigen), C.F IL-1β (cystic fluid interleukin1beta).

Univariate analysis showed that 4 parameters were significantly predictive for risk of malignancy in pancreatic cyst. They were age, site of cyst, tumor size, and C.F IL-1β. These 4 significant factors of malignancy in PCLs detected in univariate analysis were additionally analyzed in multivariate analysis.

The multivariate analysis showed that only 2 factors (tumor size, and C.F IL-1β) were significant $P < 0.05$ (Table 4). There was a significant statistical difference between mucinous and non-mucinous pancreatic cysts as regard C.F CEA and C.F IL-1β (Table 5).

Table 4. Multivariate analysis of significant factors associated with risk of malignancy in the pancreatic cyst.

	B	S.E.	Wald	*P*-value	Odds ratio (OR)	95% C.I. for OR	
						Lower	Upper
Age >58 years	2.018	0.77	6.859	0.009	7.522	1.662	34.056
C.F IL-1β >150 pg/ml	1.367	0.739	3.425	NS	3.922	0.922	16.68

OR: Odds ratio, CI: Confidence interval. $P > 0.05$ is not significant (NS).

Table 5. Comparison between mucinous and non-mucinous cysts as regard to studied biochemical test.

		Non-mucinous	Mucinous	*P*-value
		No. = 26	No. = 24	
C.F amylase u/l	Median (IQR)	6490.5 (342 – 18765)	1832 (1184 – 3276)	NS
	Range	12 – 32196	112 – 14794	
C.F CEA ng/ml	Median (IQR)	3.5 (1.43 – 8)	429 (248.5 – 634.5)	0.000
	Range	0.77 – 90	71 – 2361	
C.F IL-1β pg/ml	Median (IQR)	150 (100 – 250)	275 (200 – 550)	0.005
	Range	0 – 1250	50 – 8000	
Mucin stain	Negative	26 (100.0%)	0 (0.0%)	0.000
	Positive	0 (0.0%)	24 (100.0%	

C.F CEA (cystic fluid carcinoembryonic antigen), C.F IL-1β (cystic fluid interleukin 1 beta). *: Chi-square test; **: Mann-Whitney test; $P > 0.05$ is not significant (NS).

The cutoff value of IL-1β in differentiating between mucinous and non-mucinous cysts was >150 pg/ml, with a sensitivity and specificity of 83.33% and 53.78%, respectively. The cutoff value of CEA in differentiating between mucinous and non-mucinous cysts was >65 ng/ml with a sensitivity and specificity of 100% and 96.15%, respectively (Figure 2).

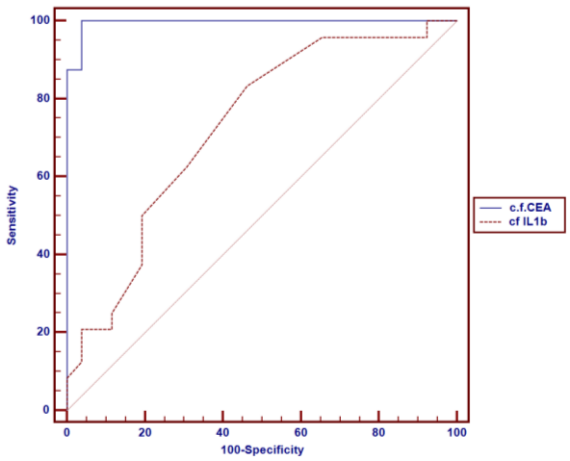

Figure 2. ROC curve analysis of C. F IL-1β and C.F CEA to distinguish between mucinous and non-mucinous cysts. C.F CEA (cystic fluid carcinoembryonic antigen), C.F IL-1β (cystic fluid interleukin1 beta).

Univariate analysis found 4 values to be significantly predictive of mucinous cysts (age, site, size of cyst, and C.F IL-1β). These 4 predictive values of mucinous cysts in PCLs detected in univariate analysis were additionally analyzed in multivariate analysis. The values for these 4 values (age, site, tumor size, and C.F IL-1β) in the multivariate analysis were significant $P < 0.05$ [Table 6]. There was no difference between high and low grade IPMN as regard C.F.CEA, C.F. IL-1β.

Table 6. Multivariate analysis of significant factors associated with mucinous cysts.

	B	S.E.	Wald	*P*-value	Odds ratio (OR)	95% C.I. for OR	
						Lower	Upper
Age >58ys	1.982	0.947	4.385	0.036	7.260	1.135	46.427
Pancreatic head	0.045	0.845	0.003	NS	1.046	0.200	5.483
Pancreatic body	-0.858	0.969	0.784	NS	0.424	0.063	2.832
Size of cyst ≤ 80 mm	0.779	1.065	0.536	NS	2.180	0.270	17.578
C.F IL-1β >150 pg/ml	0.534	0.851	0.394	NS	1.706	0.322	9.035

OR: Odds ratio, CI: Confidence interval. B: regression constant. S.E: standard error. Wald test of significant

P > 0.05 is not significant (NS).

Table 7. Comparison between high and low-grade IPMN lesions as regard to studied biochemical tests.

		Low grade dysplasia	High grade dysplasia	*P*-value
		No. = 3	No. = 9	
C.F.CEA ng/ml	Median (IQR)	367 (112 – 440)	267 (86 – 356)	NS
	Range	112 – 440	71 – 550	
C.F. IL-1β pg/ml	Median (IQR)	300 (200 – 500)	800 (500 – 1250)	NS
	Range	200 – 500	250 – 8000	

P > 0.05 is not significant (NS). **: Mann-Whitney test.

Discussion

PCLs are now more frequently detected with the increased use of abdominal MRI and CT imaging.[11] Some of these PCLs have a risk of malignancy.[12] Thus, considering the efficacy of pancreatic excision, it is not surprising that the number of excisions for PCLs has increased. Pancreatic excision can remove symptomatic, potentially malignant, or malignant lesions. Although, some pancreatic cystic lesions are slowly growing or benign, and their risk for malignancy still unclear.[11] Some studies have found that only one-fifth of the excised asymptomatic pancreatic cysts are malignant.[13] Surgeons need a fast and accurate assessment of the risk-benefit ratio of follow-up versus excision of these neoplasms in every patient. The recently available tools are defective at answering these two questions i) how to distinguish MCNs and IPMNs from other benign cysts of pancreatic cysts which require no surveillance; ii) how to distinguish MCNs and IPMNs which have high-grade dysplasia or an associated with a high risk of invasive pancreatic adenocarcinoma and require surgical excision from MCNs and IPMNs which can be safely followed.[13]

This is established in many surgical studies, as over 20% of patients are being of low-risk cysts, while up to 78% of resected IPMNs do not have high-grade dysplasia or invasive adenocarcinoma.[14] Thus, differentiating serous cystadenomas (SCAs) from MCNs and IPMNs is necessary if needless follow-up or surgical excision to be avoided.

SCAs, which are mostly located in the tail or body of the pancreas, exist most commonly in elderly women. In contrast, IPMN exists mostly in elderly male patients in the pancreatic head,

and mucinous cystadenomas exist more in middle-aged females.[15] In our study, sex could not be considered a risk factor for malignant pancreatic cystic neoplasms (PCNs), and this goes with Lan et al., 2018.[16] However, such observation did not agree with data of a study by Atef et al., 2013,[17] and by Lee et al., 2008,[18] who showed that the overall risk of malignancy was higher in men.

Our study showed that older age was significantly associated with malignancy (*P*=0.00) and this goes with that reported by Lan et al., 2018,[16] and by Spinelli et al., 2004[13] who found that age more than 70 years was a risk factor for having malignant cysts. Similarly, several studies also found that the risk of malignancy in MCN and IPMN was higher in older patients 19 20 21.

Our study showed that cyst size was significantly different between benign and malignant cysts, as the large cyst diameter was significantly greater in the benign cysts (73.08 ± 30.40 mm) as compared with malignant cysts (48.14 ± 17.71 mm) (*P* = 0.006). This did not agree with that reported by Lan et al., 2018[16] who showed that large cyst diameter, in the malignant pancreatic cysts, was significantly greater as compared with benign cysts. Furthermore, studies by Spinelli et al., 2004.[13] and by Sarr et al., 2000,[21] found that cyst diameter did not correlate with final pathology. In another study, Chari et al., 2002,[22] found that IPMN was 5.2 cm in diameter in their 73 noninvasive, while IPMN was 6.6 cm their 40 invasive. Another study by Lee et al., 2008,[18] found that patients with cystic pancreatic tumors < 3 cm had malignancy. Such observation agreed with the results of other studies, reported that malignancy rates ranged between 13 and 20 % in small lesions.[23] Thus, cysts of small diameter do not preclude its malignant risk, but malignancy is more with increased cyst diameter. Since our study included all pancreatic cyst types, this may explain the difference in findings between our study and others.

In our study site of the pancreatic cystic lesions could not predict malignant lesions but most the IPMN neoplasms were present in the head of the pancreas, and this agreed with that of Lan et al., 2018,[16] and Atef et al., 2013.[17]

Our study showed that cyst fluid IL-1β can differentiate between benign and malignant cyst in cystic fluid analysis (*P*= 0.00) but could not differentiate between high and low-grade IPMN. Such observation did not agree with that of Maker et al., 2011,[24] who found that IL-1β differentiated high- from low-risk cysts. Also, our finding did not agree with that of Simpson et al., 2019,[25] who found that Level of IL-1β were higher in high-grade dysplasia.

We observed that cyst fluid IL-1β can differentiate between both mucinous and non-mucinous pancreatic cysts and this agreed with Maker et al., 2011,[24] who found that IL-1β levels measured in non-mucinous serous cystadenomas were barely detectable.

Our study showed that cyst fluid CEA can differentiate between mucinous and non-mucinous and between benign and malignant cysts but cannot differentiate between degrees of dysplasia of IPMN. This is not in agreement with Maker et al., 2011,[24] or with Khalid et al., 2009, [26] who found that pancreatic cyst fluid CEA levels do not associate with the presence or absence of malignancy. Such observation was settled in a large-scale, prospective multicenter PANDA trial as reported by Khalid et al., 2009,[26] but it can differentiate between mucinous and non-mucinous cyst.

A study by Pais et al., 2007,[27] found that no difference in CEA between benign and malignant pancreatic cysts. Although, CEA levels in benign and malignant cysts overlap significantly, which means that any cut-off threshold value used would suffer from a large number of false positives or false negatives, limiting its use.

In conclusion, this study showed that preoperative clinical findings such as patient's age, size of tumor, cyst fluid IL-1β can predict risk of malignancy in the pancreatic cysts. Cystic fluid CEA and IL-1β can differentiate between mucinous and non-mucinous cysts, and between benign, and malignant cysts but cannot differentiate between degrees of IPMN dysplasia.

Author Contributions

TA is the corresponding author and contributed interpretation of the results and helped in editing the manuscript and reference collection. SM revised the manuscript. AA revised the manuscript. TM shared in manuscript revision and writing. SA contributed to the data collection and analysis, reviewing the literature, shared in statistical analysis, helped in manuscript editing. HH contributed to the data collection and analysis and shared in manuscript revision and writing. MZ shared in statistical analysis. MG contributed to the data collection and analysis. MA shared in manuscript revision and writing. All authors have read and approved the final version submitted.

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Research Faculty of Medicine Ain Shams University (FMASU, MD 331/2018).

Informed consent

An informed consent was obtained from each participant before included in the study.

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