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João Artur Ferreira Freitas Coimbra

A systematic review on CA19.9, CEA and amylase in pancreatic cystic lesions

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PROJETO DE OPÇÃO
DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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Faculdade de Medicina da Universidade do Porto, 20 / 3 / 2012

Assinatura: _____

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A systematic review on CA 19.9, CEA and amylase in pancreatic cystic lesions

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Keywords: pancreatic cystic lesions, fine-needle aspiration, CA 19-9, CEA, amylase

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Abstract

Background: Pancreatic cystic lesions are commonly diagnosed and most importantly present a wide range of prognosis and different management namely for serous versus mucinous lesions. Intra-cystic tumor markers such as CEA and CA19.9 and amylase enzyme seem to be valuable to discern pancreatic cystic lesions but no definitive cut-off value has been proposed. Aim: To determine the best cut-off value to discern non-mucinous from mucinous pancreatic neoplasms. Design: Systematic review and meta-analysis of sensitivity and specificity, hierarchical summary receiver-operating characteristic (HSROC) curve. Setting: Manuscripts in *MedLine* published until January 2012. Patients: Patients with cystic pancreatic lesions. Interventions: CEA, CA19.9 and amylase values from pancreatic cystic fluid after fine-needle aspiration through CT scan or EUS. Main Outcome measurements: Surgical specimens' histopathological results. Results: Twenty articles and 1080 patients were included. A wide range of cut-off values was noticeable with CA19.9 ranging from 150 to 50000U/mL and CEA cut-off values from 3 to 480μg/mL. CEA>400μg/mL (used in n=3 studies) and CA19.9>37 U/mL (also in 3 studies) showed the highest DOR with 112.83 and 25.07, respectively, to discern mucinous and serous lesions of pancreas. CEA>400μg/mL presents with a very high specificity of 99% whereas the pooled sensitivity for CA19.9>37U/mL showed 84% and 82% of sensitivity and specificity, respectively. Amylase has a DOR of 9.62 for discerning PC from other lesions. Limitations: Inadequate description of data in most original articles and search in a single database. Conclusions: Even though, heterogeneity in literature, CEA>400μg/mL and CEA 19.9 > 37U/mL may strongly suggest mucinous pancreatic cystic neoplasm. Amylase may be also helpful to distinguish pseudocysts and other pancreatic cystic lesions. Multicentre registries would be welcome to better clarify this issue in the future, namely by addressing the 3 markers altogether.

Introduction

Pancreatic cystic lesions (PCL) may be benign (pseudocysts and serous cystadenomas), premalignant (mucinous cystadenomas) or malignant (mucinous cystadenocarcinomas).

The difference between mucinous neoplasms and non-mucinous neoplasms must be recognized because treatment differs. Pseudocysts (PC) require no treatment if it is asymptomatic. Serous cystadenoma (SCA) are benign lesions and should not be resected. Mucinous cystadenoma (MC) and mucinous cystadenocarcinoma (MCAC) have a surgical treatment because it is pre-malignant and malignant, respectively(1).

Diagnose PCL is actually more frequent than few years ago because advances in imaging diagnostic techniques(2). However, neither clinical presentation nor imaging procedures are sufficient to discern the different types of lesions. The classic cross-sectional images, computed tomography (CT) scan or ultrasonography, cannot supply a definite diagnosis (3). Also, EUS can show detailed images of the cystic wall and septations (4), but mucinous from non-mucinous pancreatic lesions can in general be differentiated without a EUS-FNA is used to collect the cystic fluid and some markers used to discern between lesions.

Nevertheless, guidelines (5) have been published suggesting the results of the single literature review (6) shown that CEA>800ng/mL can be used discern mucinous lesions from other cystic lesions with 48% of sensitivity and 98% of specificity.

We aimed at updating that review and to search for CEA and other markers in the literature to establish a cut-off points that allow discerning the benign and pre-malignant or malignant mucinous pancreatic cystic lesions.

Methods

A. Type of study

A systematically review using PubMed was performed independently by two researchers (JFC and PPN) between 2004 (the last date for manuscripts included in the review we aimed at updating and that it was used in guidelines) to January 2012. A boolean search strategy was used for PubMed [i.e., Cyst, pancreas, AND fluid AND (Humans [Mesh] AND (English [lang] OR Portuguese [lang]) AND ("2004/06"[PDat] : "2012/01"[PDat]))]. Manuscrits included were added to the list of references used in the previous manuscript.

B. Inclusion Criteria

Studies were identified on a priori criteria that included: (1) pancreatic cystic neoplasms, (2) tumor markers collected and (3) histologically confirmed diagnosis. Studies addressing less than seven patients or studies published in other languages than English were excluded.

C. Data extraction

Data was extracted from each study by the leader investigator and entered into a computerized database. Type of study (retrospective, prospective), number of patients, female percentage of patients, technology used (CT, EUS or other), tumor markers (eg. CEA, CA19.9) and amylase, and respective different cut-off values used in different studies was collected. . Specific data regarding the cutoff value evaluated, the sensitivity/specificity, and the positive/negative predictive value for the diagnosis were also included. Again the reason to focus on CEA and CA19.9 was justified by the previous manuscript and recent guidelines.

D. Statistical Analysis

We aimed at, whenever homogeneity was present, to pool the results in summary sensitivities, specificities, and diagnostic odds ratio (DOR) to be used to examine the CEA, CA19.9 and amylase levels accuracy for the differentiation of differentiation between pancreatic cystic lesions, namely between neoplastic lesions and between pseudocysts and other. Review Manager version 5.1 and Metadas, version 1.3, from SAS were used for the analysis. For all studies the counts used for the calculation of 2 × 2 tables were deduced from reported sensitivity, specificity, disease prevalence, and total number of patients studied. DOR expresses how much bigger the odds of having the disease are for the people with a positive test result than for the patients with a negative test result. Hierarchical summary receiver operating characteristic (HSROC), that plots sensitivity versus specificity, curve was also constructed to graphically present the results.

Results

A. Selected manuscripts

Twenty articles and 1080 patients were included, according inclusion criteria (Figure 1). The number of patients varied from 7 to 126 (median 38); all but one study (7) study shown that mucinous cystic lesions are more frequent in women (51% to 88%, media 64%). The oldest paper was published in 1986 and the last one in 2011. From 2002, FNA mode is consistently EUS but in previous studies there was used US, CT and intraoperative aspiration. Many studies used both Ca19.9, CEA and amylase, but other studies analyzed only one marker. Also, amylase was assessed in 6 studies of those 5 established not only differentiate mucinous and non-mucinous cystic lesions but also pseudocysts for further cystic lesions. Some studies consider one or more cut-off points to the same marker or enzyme. We consider this values as two or more different tests in our data analyzes.

B. CEA

For CEA analysis, in the 20 articles (table 1), 14 different cut-off values were considered ranging from 3µg/mL to 480µg/mL (Table 2). CEA >400µg/mL has a specificity of 99% to diagnose mucinous cystic neoplasms and it has sensitivity of 39%. Cut-off value of 5µg/mL is more sensible 83% but low specific 58%; however the DOR is the lowest (6.4), Using a cut-off value of 192µg/mL it is possible to obtain a sensitivity of 75% and specificity of 78%. Increasing cut-off CEA values the specificity and DOR of CEA grows, but the sensitivity decreases. If CEA<5µg/mL would be considered as suggested by European Gastroenterology Society Guidelines(5) sensitivity of 58% specificity of 83% and a DOR of 6.43, would be noticeable.

C. CA19.9

For CA19.9 data from ten articles (table 1) were analyzed, which contains 6 different cut-off values

(Table 2), ranging from 150U/mL to 50000U/mL CA19.9 >37U/mL, used in 3 studies, has sensitivity and specificity of 84% and 82%, respectively, to discern mucinous cystic lesions among pancreatic cystic lesions. With this cut-off value DOR is 25.1. CA19.9 cut-off 50.000U/mL present specificity of 91% and sensitivity of 66% and a diagnostic odd ratio of 20.3.

D. Amylase

Amylase data were collected from 6 studies where this marker was used to distinguish between pseudocysts and whole other lesions. However, 5 studies allowing discerns mucinous and non-mucinous lesions. Amylase showing a DOR of 9.62 for discerning PC from other lesions and a DOR of 0.49 for distinguish mucinous and non-mucinous cystic lesions.

E. Other results

We analyze if there is a FNA mode that can influence the results trough a covariate analyze. After that we know, using different methods for FNA, specificity, sensitivity and DOR are the same independently of FNA mode. Different needle gauges (19G, 22G and 25G) were used in studies (Table 1). We tested if needle gauge could make difference is the measure of analyzed tumor markers. We obtained no differences among different needles.

We obtained that there are no significantly differences between different methods of collecting cyst fluid for analyses.

Discussion

Pancreatic cystic lesions account about 1% of pancreatic cystic tumors(8). The majority of the cystic lesions are pseudocysts and comprises 80% to 90% (9) of PCL. PC can be suspected if acute pancreatitis occurred previously and/or chronic pancreatitis lesions are showed (10). Serous cystadenomas are composed by a cuboidal epithelium that contains glycogen. On the other hand, mucinous cystic neoplasms are involved by a columnar epithelium that is full of mucin secreting cells (1). The diagnosis is difficult: one third of pancreatic cysts are misdiagnosed as pseudocysts (11).

The difference between mucinous neoplasms and non-mucinous neoplasms might be recognized because treatment differs(12, 13). Pseudocysts require no treatment if it is asymptomatic. Otherwise can cause symptoms of pain and recurrent pancreatitis and have to be drained (14). It can be treated by endoscopic cystogastrostomy. SCA are benign lesions and should not be resected(15) unless symptomatic. Mucinous cystadenoma and mucinous cystadenocarcinoma have a surgical treatment because it is pre-malignant and malignant, respectively. The pre-malignant type of lesion could turn malignant over time (1).

Diagnose PCL is actually more frequent than few years ago because advances in imaging diagnostic techniques (14). But imaging and clinical procedures are not sufficient to discern the different types of lesions (16) The classic cross-sectional images cannot supply a diagnostic.

Although EUS, which was introduced in 1980, can show detailed images of the wall and septations (4), it isn't enough to do a diagnosis (13). Many studies propose that EUS alone cannot differentiate mucinous cystic neoplasms from other non-mucinous pancreatic lesions (1, 6, 17-19). In other hand some studies suggest that the clinical and radiologic studies are reliable (10) and tumor markers dosage are not essential.

Around 1995, EUS-FNA was introduced and has now become an essential diagnostic modality for PCL in order to analyze the cystic fluid. Since that, many different investigators tried different

methodologies to show the differences in PCL. CEA is the most often used. Other markers like CA72-4, CA125 (20), amylase (21), lipase (21), elastase 1 (14), GGT (21), k-ras (8), p53 (8), pancreatitis-associated proteins (10). Viscosity was also tried (20).

Centeno et al. (22) in contrast with the results of Pinto and Meriano (23)conclude that a EUS-FNA cytology analysis is a sensitive and specific method for preoperative evaluation of pancreatic cysts. Brugge et al (1) suggest EUS-FNA cytology has limited efficacy because obtaining cells for diagnostic through a needle to cytology may bring insufficient cells. Histology could bring some misdiagnosis especially in the serous and mucinous cystadenomas because there are a small number of cells in those cysts (17).

There are no a general understanding about the diagnostic and management of pancreatic cystic lesions. The challenge remains due to the importance of tumor markers. In our study we analyze CEA and CA19.9 performance.

Based on the literature revision and meta-analysis, our aim is to evaluate the tumor markers potential in the differentiation of mucinous cystic neoplasm and to establish a cut-off value that could help to decision-making in PCL (11).

Hammel (21), Pinto and Meriano (23), Tatsuta et al (14) recommended the fluid analyzes for tumor markers and biochemical analyzes as a method to differentiate the PCL. Lewandrowski et al. were the first who demonstrated that mucinous neoplasm had CEA high concentration. Diagnosis using CEA values is also useful because its values are different in mucinous lesions and serous cystadenomas or pseudocysts. Moreover CEA is available to make a distinction from serous cystadenomas to pseudocysts, according some authors (17).

In our study, different cut-off values were tested (table 2). CEA showed the best specificity (99%) when cut-off 400µg/mL was used, but best sensitivity appears when cut-off 5µg/mL (83%). Intermediate cut-off value of 192µg/mL shows good sensitivity (75%) and specificity (78%). Using diagnostic odds ratio (DOR) we showed CEA 400µg/mL as the best test to differentiate mucinous and non-mucinous pancreatic cystic lesions. So it suggests that CEA >400µg/mL is better in

diagnostic making of mucinous cystic neoplasm of pancreas.

European Gastroenterology Society Guidelines (EGSG) (5) suggest that CEA>800μg/mL could be used to identify mucinous cystic lesions with 98% of specificity and 48% of sensitivity. After current study we recommend to use CEA>400μg/mL, in order to discern mucinous and non-mucinous lesions, introducing more specificity in diagnose (99%) with a minor lack of sensitivity. Using CEA>400μg/mL many patients could be correctly identified as having a mucinous cystic lesion and simultaneously a CEA dosage between 400μg/mL and 800μg/mL.

Also according with EGSG we tested the potential of CEA<5μg/mL to identify benign lesions (PC and serous cysts). We obtained sensitivity of 58% and specificity of 82.5% (50% and 95%, respectively at EGSG). This cut-off value shows a DOR of 6.44 that reveals this is not a good test to identify benign lesions, although it has a good sensitivity.

Some authors refers that intra-cystic CA19.9 has not been found to be a discriminatory marker for cystic pancreatic tumor (10, 24) probably because of the high levels observed in pseudocyst (24). Cyst fluid CA19.9 concentration did not differ in the patients with pseudocysts plus serous cystadenomas and those with mucinous cysts (10). The values of CA19.9 are too overlapped in the PCL, according other authors (14, 20).

We analyze nine diagnostic tests using CA19.9 the cut-off values of 37U/mL and 50.000U/mL that had a sensitivity of 84% and 66% and a specificity of 82% and 91%, respectively. The best DOR appears with 37U/mL cut-off value, which means that is the best to discriminate mucinous and non-mucinous cut-off values.

Amylase appears to be better to make evidence of pseudocyst than to recognize mucinous and non-mucinous cystic lesions. We obtained a DOR of 9.62 for distinguish pseudocyst from other pancreatic cystic lesions. Amylase could not be used to discern mucinous and non-mucinous lesions.

We tested the influence of FNA methodology in the results. We prove that there are no influences in results of the methods of FNA. In spite of being more recently used and it could bring more facilities in punction, there are no statistically differences in using EUS than US, CT or other

method.

Further studies should be necessary to explain clearly which role cystic CEA and CA19.9 have in the diagnostic of pancreatic cystic lesions. A large multicenter prospective study should be important to explain better the role of CEA and CA19.9. Large studies involving new diagnostic methods (like DNA mutations analyzes, proteomic analyzes and other new methods) could be performed in order to know better how to do a correct diagnostic of pancreatic cystic lesions.

Disclosure

There are no conflicts of interest noted in article authors.

Tables and Figures Legends

Table 1: Studies selected according to type of study, imaging procedure used for FNA and sample size. Percentage of female and the median or mean age of participants is presented as well the needle type and markers assessed [na: not addressed; US – ultrasonography EUS: endoultrassonography; CT: computed tomography; *Analyzes with 27 patients; to our analyzes we only use the 20 patients that had tumor marker measurement; # not used for amylase analyze]

Table 2

CEA, CA19.9 and amylase cut-off values and respective sensitivities, specificities, likelihood positive and negative ratios and diagnostic odds ratio for discerning mucinous and non-mucinous pancreatic lesions. n= number of studies

Figure 1

Diagram of the main characteristics of the studies included in the meta-analysis..

Figure 2

Hierarchical summary receiver-operating characteristic curve of the sensitivity versus specificity of CEA cut-off 400µg/mL for discerning mucinous and non-mucinous pancreatic lesions The curve is represented by the straight line; each of the analyzed studies is represented by a square; the point estimate that summary sensitivity and specificity correspond to is represented by the circle shape and the respective 95% confidence intervals by the dashed line, whereas the 95% confidence area in which a new study will be located is represented by the dotted line.

Figure 3

Hierarchical summary receiver-operating characteristic curve of the sensitivity versus specificity of CA19.9 cut-off 37U/mL for discerning mucinous and non-mucinous pancreatic lesions The curve is represented by the straight line; each of the analyzed studies is represented by a square; the point estimate that summary sensitivity and specificity correspond to is represented by the circle shape and the respective 95% confidence intervals by the dashed line, whereas the 95% confidence area in which a new study will be located is represented by the dotted line.

Figure 4

Forest plot of pooled sensitivity and specificity of CA19.9 cut-off 37U/mL for discerning mucinous and non-mucinous pancreatic lesions. The point estimates and the respective 95% confidence intervals for each one of the included studies are represented by the squares and the horizontal lines.

Figure 5

Forest plot of pooled sensitivity and specificity of CA19.9 cut-off 50000U/mL for discerning mucinous and non-mucinous pancreatic lesions. The point estimates and the respective 95% confidence intervals for each one of the included studies are represented by the squares and the horizontal lines.

Figure 6

Forest plot of pooled sensitivity and specificity of CEA cut-off 5μg/mL for discerning mucinous and non-mucinous pancreatic lesions. The point estimates and the respective 95% confidence intervals for each one of the included studies are represented by the squares and the horizontal lines.

Figure 7

Forest plot of pooled sensitivity and specificity of CEA cut-off 192μg/mL for discerning mucinous and non-mucinous pancreatic lesions. The point estimates and the respective 95% confidence intervals for each one of the included studies are represented by the squares and the horizontal lines.

Figure 8

Forest plot of pooled sensitivity and specificity of CEA cut-off 400μg/mL for discerning mucinous and non-mucinous pancreatic lesions. The point estimates and the respective 95% confidence intervals for each one of the included studies are represented by the squares and the horizontal lines.

Table 1

	Participants			FNA procedure	
	n	Female (%)	Age	Needle	Markers
Prospective					
EUS					
Brugge et al 2004 (1)	112	63	60	19/22G	CEA, CA19.9
Hammel et al, 1998 (11)	91	na	na	19G	CEA
Frossard et al, 2003(17)	67	61	59	22G	CEA, CA19.9, amylase
Shami et al, 2007 (25)	35	56	63	19/22G	CEA
US					
Lewandrowski et al, 1993 (20)	25	73	na	Intra-operative, 22G	CEA, CA19.9, amylase
Sand et al, 1996(10)	24	59	43	Intra-operative	CEA, amylase
Tatsuta et al, 1986 (14)	17	na	na	22G	CEA
CT scan					
Hammel et al, 1998 (11)	91	na	na	19G	CEA
Hammel et al, 1995 (21)	43	na	na	19G	CEA, CA19.9, amylase
Retrospective					
EUS					
Wu et al, 2007 (26)	126	65	na	Na	CEA, CA19.9
Park et al 2011 (27)	124	na	na	na	CEA, amylase
Nagula et al 2010 (28)	97	68	65	na	CEA
Wu et al 2007 (29)	85	62	50	Na	CEA, CA19.9
Linder et al, 2006(30)	71	59	na	19/22G	CEA, CA19.9, amylase#
O'Toole et al, 2004 (18)	41	88	51	22G	CEA, CA19.9
Aljebreen et al 2007 (31)	22	71	56	22G	CEA, CA19.9
Sreenarasimhaiah et al 2009 (7)	20*	44	na	19/22G	CEA
Sawhney et al 2009 (32)	19	65	63	19/22G	CEA
Sedlack et al, 2002 (9)	7	53	55	22G	CEA
US					
Le Borgne et al, 1999(8)	27	78	57	na	CEA, CA19.9
Pinto and Meriano, 1991(23)	27	51	59	Intra-operative, 22G	CEA, amylase

Table 2

Marker and cut-off	Number of studies	Sensitivity	Specificity	LR+	LR-	DOR
CEA (ng/mL)						
5	7	0.825	0.577	1.951	0.303	6.439
192	4	0.746	0.775	3.310	0.328	10.091
400	3	0.393	0.994	68.924	0.611	112.830
CA19.9 (U/mL)						
37	3	0.843	0.823	4.773	0.190	25.075
50.000	6	0.656	0.914	7.617	0.375	20.310
Amylase	Number of tests					
Mucinous and non-mucinous lesions	5	0.310	0.436	0.691	1.400	0.493
PC and other lesions	6	0.842	0.643	2.359	0.245	9.618

Figure 1

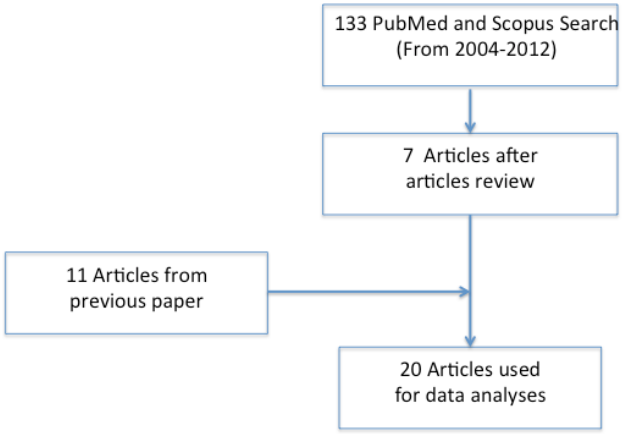
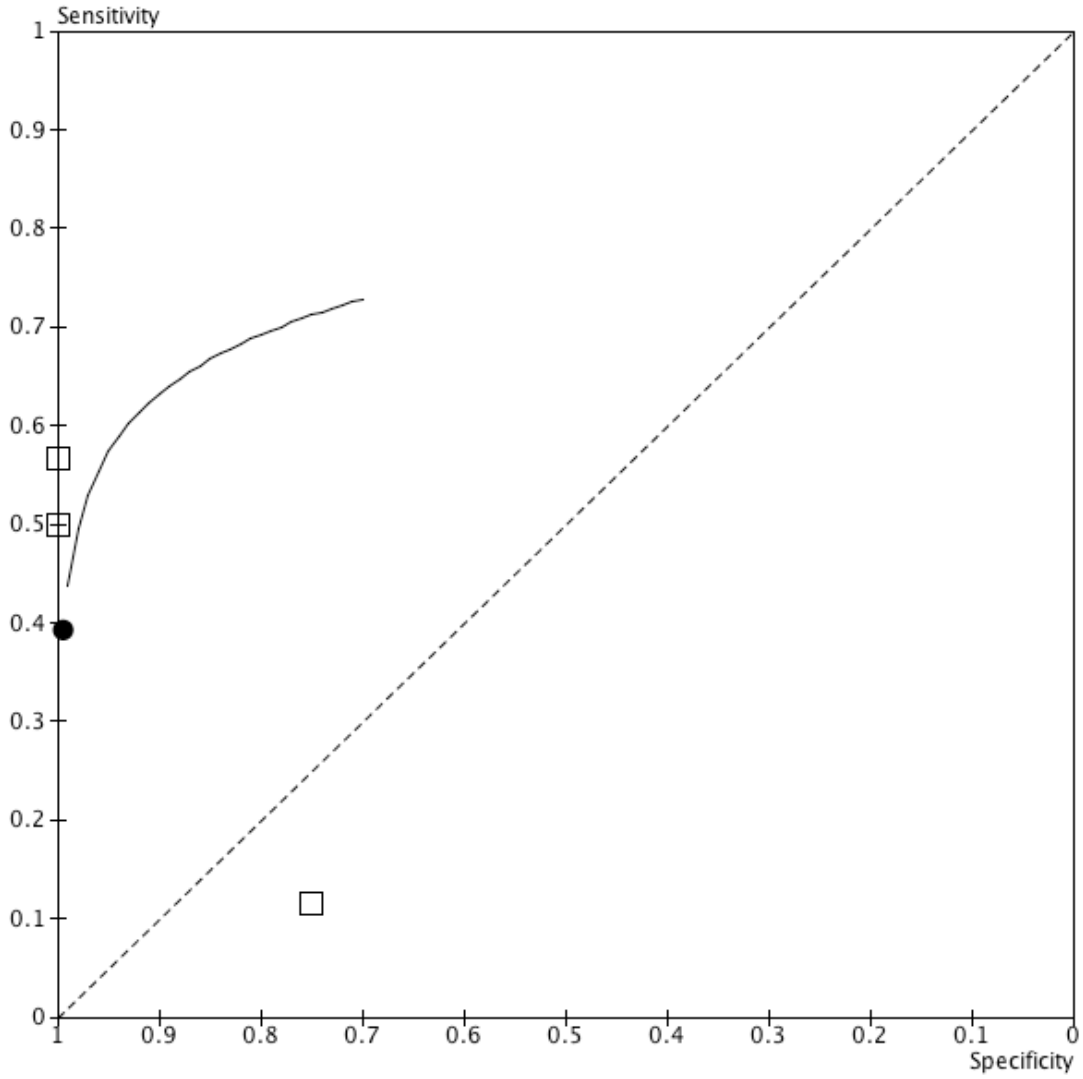

133 PubMed and Scopus Search
(From 2004-2012)
7 Articles after
articles review
11 Articles from
previous paper
20 Articles used
for data analyses

Figure 2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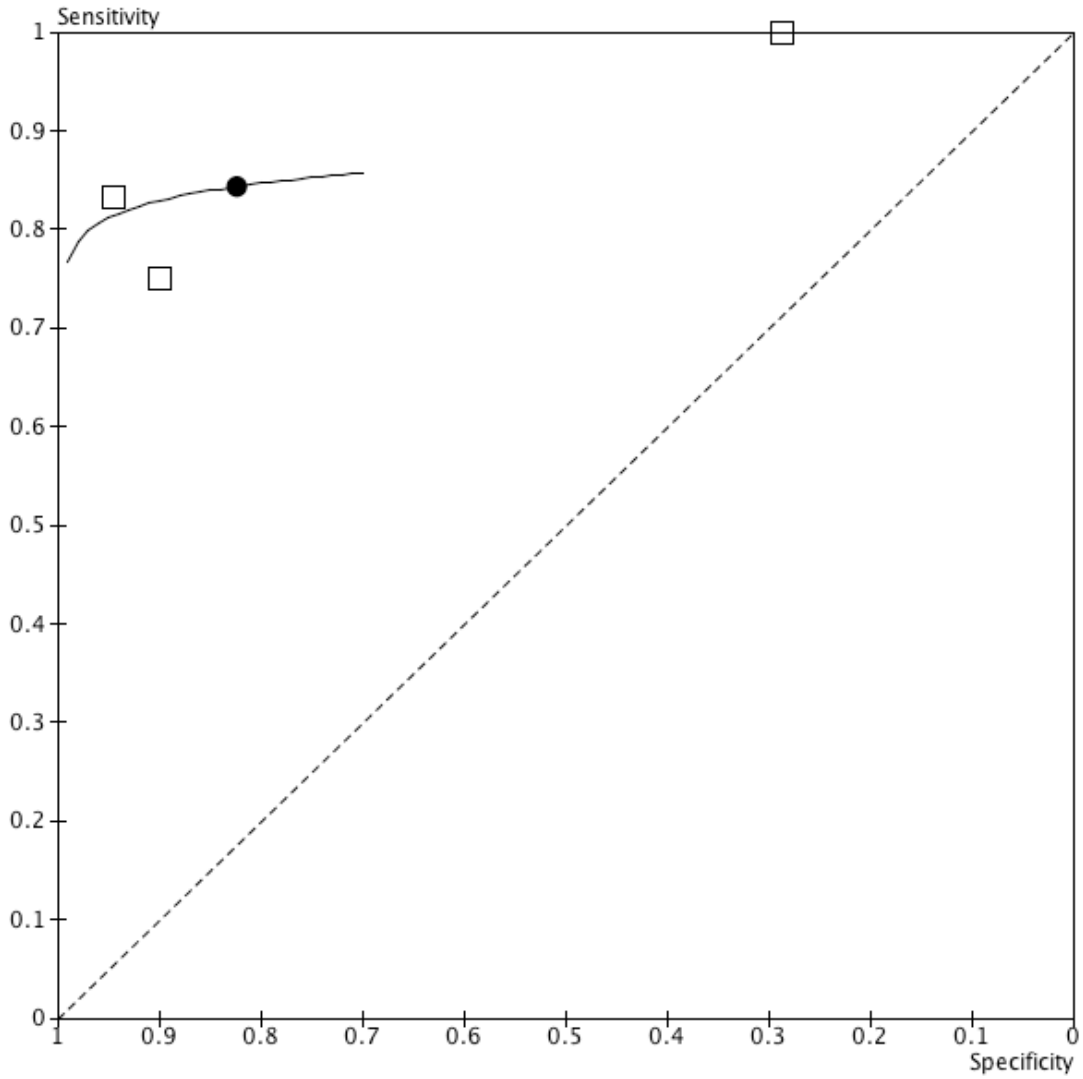
Specificity

Figure 3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Specificity

Figure 4

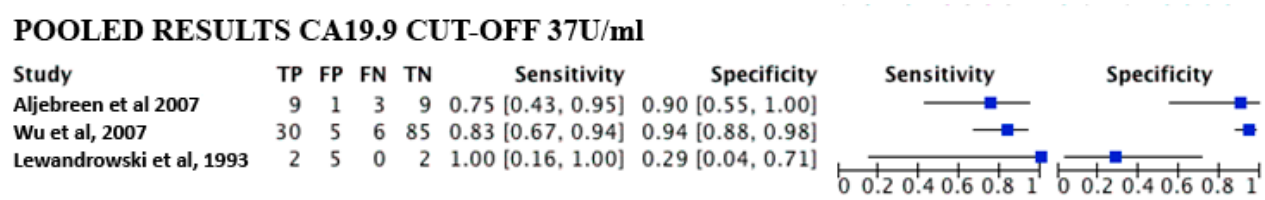
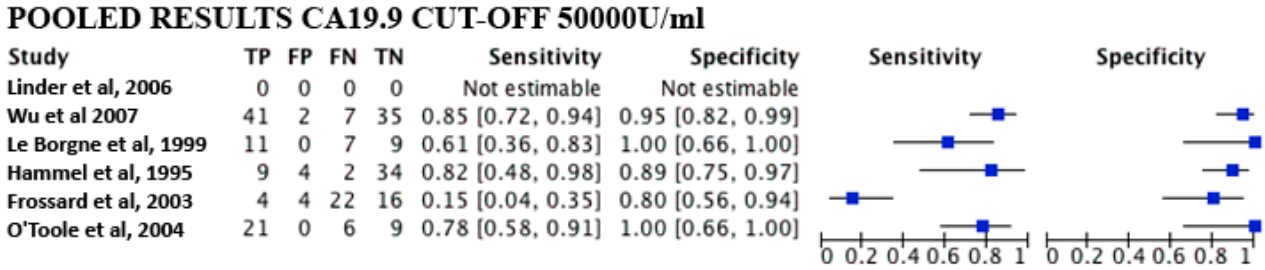


Figure 5



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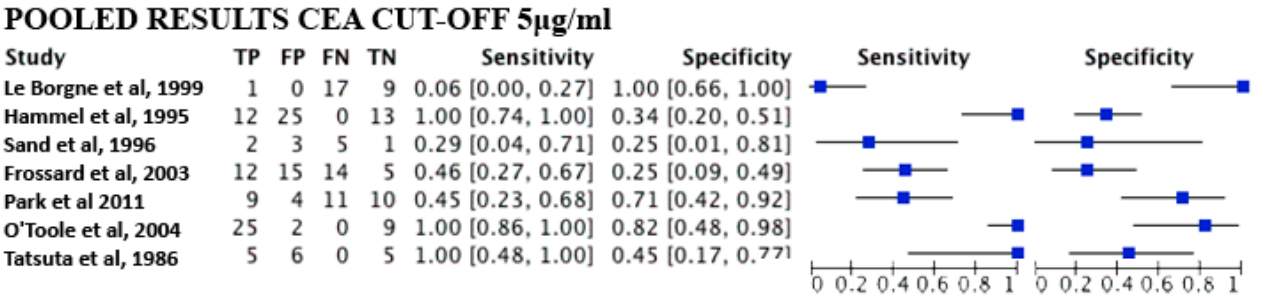

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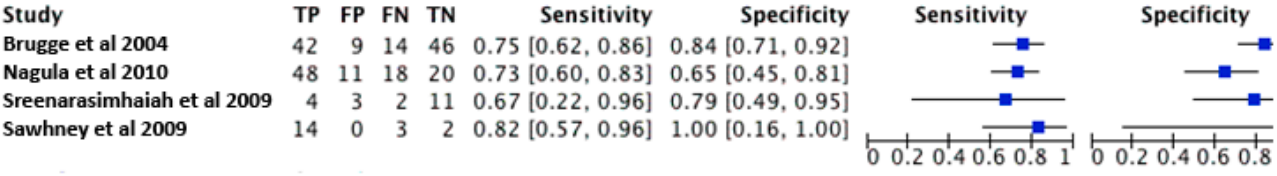
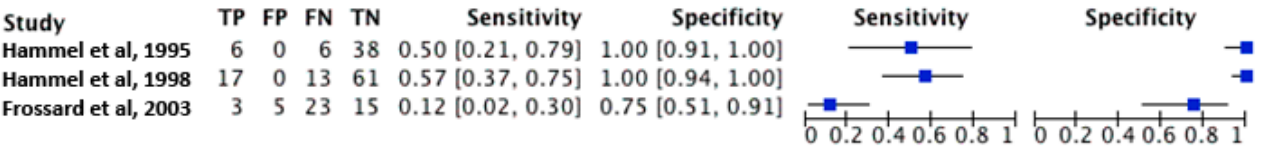


Figure 8



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