

Supplementary material

Search strategy

A comprehensive search was conducted among the main database platforms, as MEDLINE (PubMed platform), EMBASE, Cochrane platform and Web of Science Core Collection (Clarivate) to April, 2025. Keywords as “pancreatic cysts”, “intracystic glucose”, “carcinoembryonic antigen (CEA)”, “glucose levels” and “cystic fluid” were used into various strings comprehending their extended meanings. One of the used string is:

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("pancreatic cyst"[MeSH Terms] OR ("pancreatic"[All Fields] AND "cyst"[All Fields]) OR "pancreatic cyst"[All Fields] OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields])) AND ("mucine"[All Fields] OR "mucines"[All Fields] OR "mucinous"[All Fields] OR "mucins"[Supplementary Concept] OR "mucins"[All Fields] OR "mucin"[All Fields] OR "muc1 protein human"[Supplementary Concept] OR "muc1 protein human"[All Fields] OR "mucins"[MeSH Terms]) AND ("glucose"[Supplementary Concept] OR "glucose"[All Fields] OR "glucose"[MeSH Terms] OR "glucoses"[All Fields] OR "glucose s"[All Fields] OR (("intracyst"[All Fields] OR "intracystic"[All Fields]) AND ("glucose"[Supplementary Concept] OR "glucose"[All Fields] OR "glucose"[MeSH Terms] OR "glucoses"[All Fields] OR "glucose s"[All Fields])) OR (("glucose"[Supplementary Concept] OR "glucose"[All Fields] OR "glucose"[MeSH Terms] OR "glucoses"[All Fields] OR "glucose s"[All Fields]) AND ("level"[All Fields] OR "levels"[All Fields])) OR "CEA"[All Fields] OR (("intracyst"[All Fields] OR "intracystic"[All Fields]) AND "CEA"[All Fields])) AND (((("cystic"[All Fields] OR "cystical"[All Fields] OR "cystically"[All Fields] OR "cystics"[All Fields]) AND ("fluid"[All Fields] OR "fluid s"[All Fields] OR "fluids"[All Fields])) OR (("fluid"[All Fields] OR "fluid s"[All Fields] OR "fluids"[All Fields]) AND ("analysis"[MeSH Subheading] OR "analysis"[All Fields]))))"
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Definitions

Accuracy was defined as the proportion of correctly classified subjects, both those with and without the condition of interest, out of the total population examined. It is calculated as the proportion between the sum of true positive (TP) and true negative (TN) on the total number of patients (Total_n) ($\text{accuracy} = \text{TP} + \text{TN} / \text{Total}_n$). The sensitivity is the proportion of individuals with the condition who are correctly identified by the test, and it is calculated as the proportion between TP on the sum of TP and false negative (FN) ($\text{sensitivity} = \text{TP} / \text{TP} + \text{FN}$). The specificity is the proportion of individuals without the condition who are correctly classified as such, and it is calculated as the proportion of TN on the sum of TN and false positive (FP) ($\text{specificity} = \text{TN} / \text{TN} + \text{FP}$).

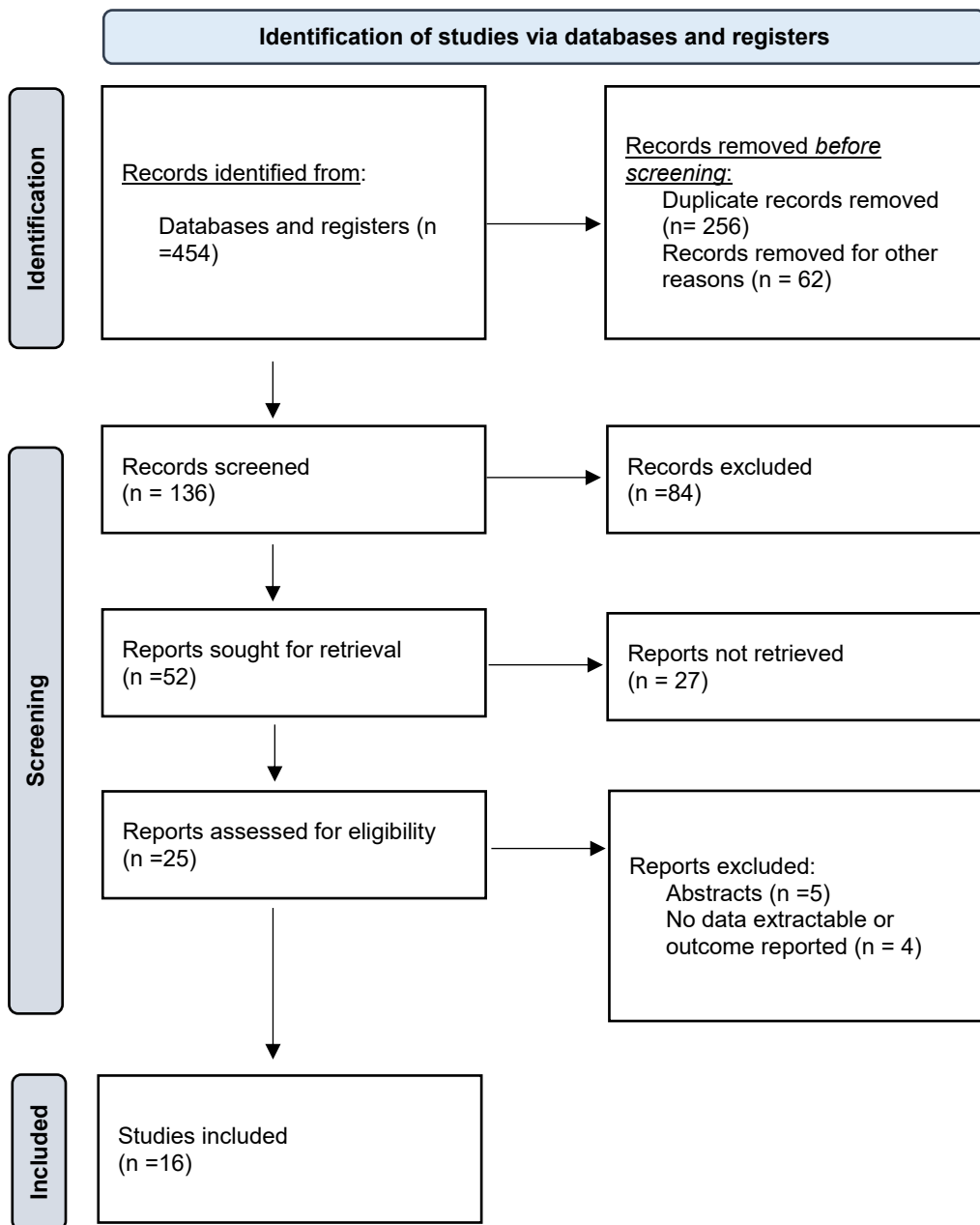
Study selection

Of 454 records initially identified through database searching, 256 duplicates and 62 records for other reasons were removed, leaving 136 titles/abstracts for screening. After excluding 84 records that did not meet the eligibility criteria, 52 full-text articles were sought for retrieval, of which 27 were not retrieved. 25 full-text articles were assessed for eligibility, and 9 were excluded. Ultimately, 16 studies fulfilled all inclusion criteria and were included in the meta-analysis.

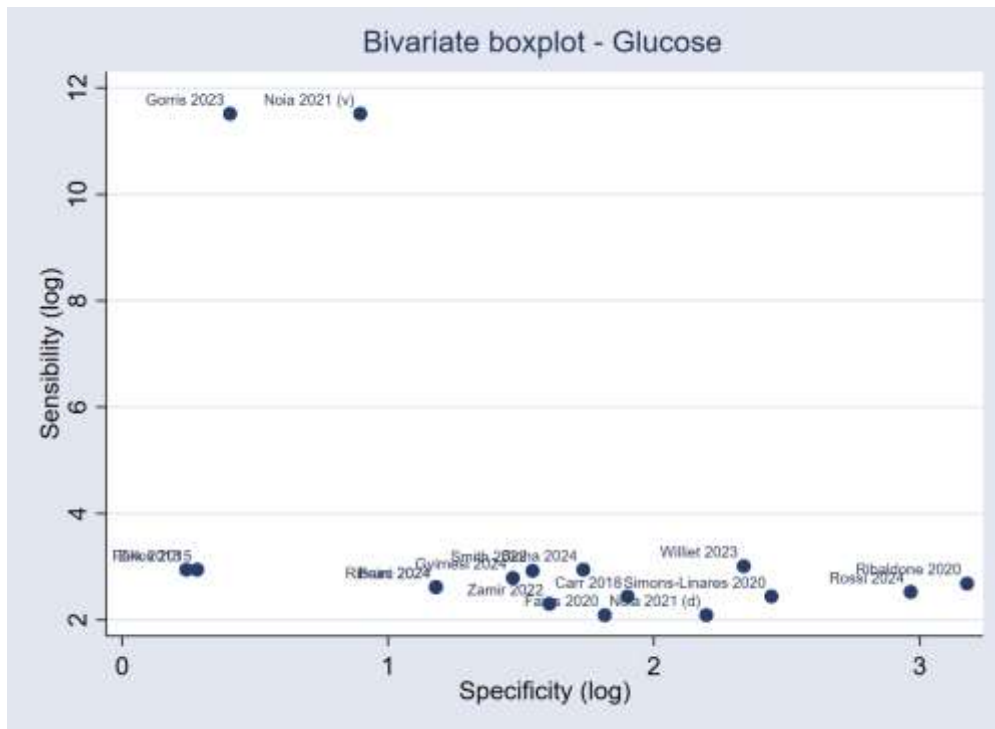
Assessment of publication bias

Publication bias was first evaluated for the meta-analysis of proportions using the doi-Galbraith plot, which revealed major asymmetry in sensitivity (LFK = 2.43) for intracystic glucose, suggesting potential publication or selection bias, whereas specificity and accuracy showed no asymmetry (LFK = 0.35 and 0.98, respectively) (**Supplementary Figures S11A - C**). For CEA, the LFK index indicated no asymmetry (0.07) for accuracy, minor asymmetry for sensitivity (LFK = 1.79), and major asymmetry for specificity (LFK = 2.10), implying possible overestimation of diagnostic performance due to selective publication of favourable results (**Supplementary Figures S11D - F**). Moreover, funnel plots and Egger's test were used for evaluating the publication bias in the comparative meta-analyses, showing risk of publication bias for accuracy when comparing glucose and CEA (Egger's test Beta= -8.74, p= 0.0298; **Supplementary figure S12A**), while no publication bias was identified for sensitivity and specificity when comparing the two markers (Beta= -0.11, p= 0.9049 and Beta= -1.58, p= 0.2512, respectively; **Supplementary figure S12B and S12C**).

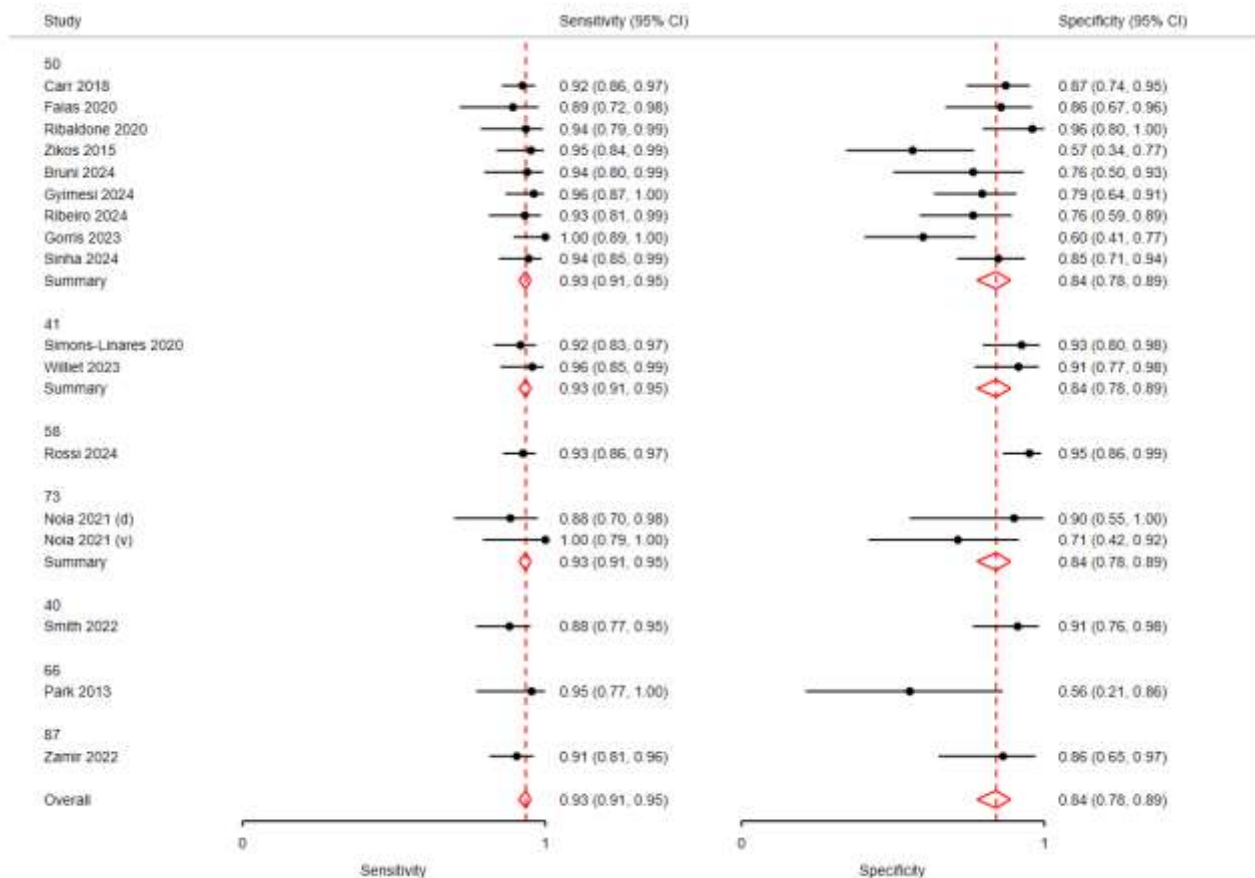
Supplementary Figures



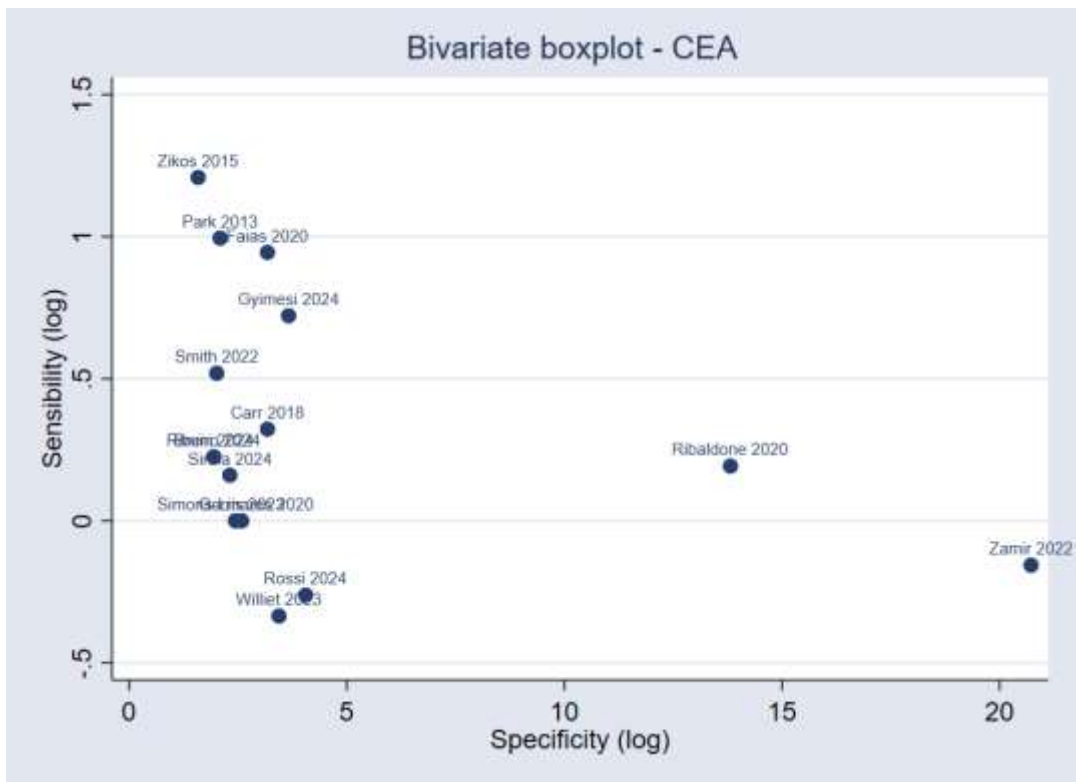
Supplementary Figure 1 PRISMA flow diagram illustrating the study selection process.



Supplementary Figure 2 Bivariate boxplot for exploring the heterogeneity of the included studies regarding the use of intracystic glucose.

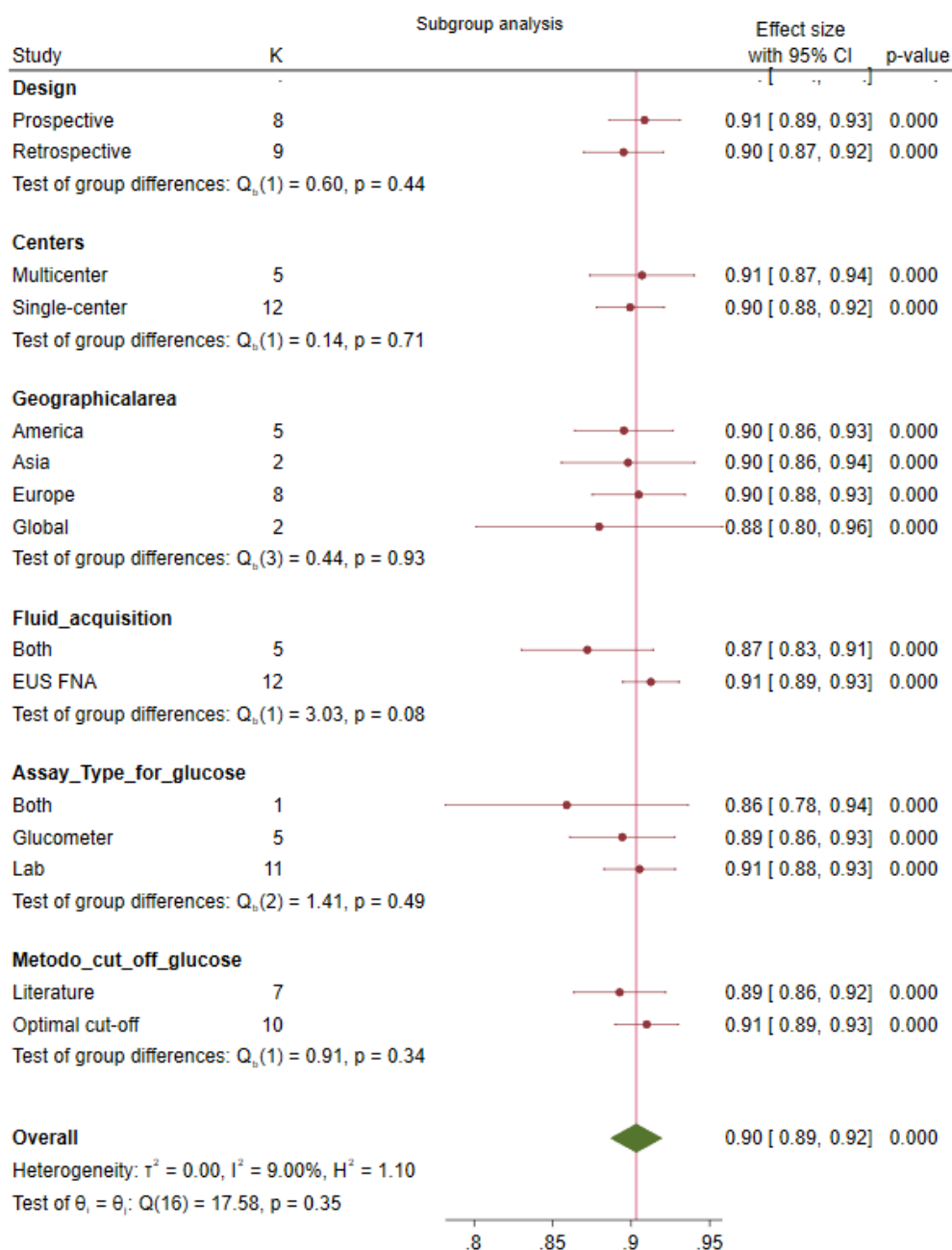


Supplementary Figure 3 Forest plot of subgroup analyses evaluating sensitivity e specificity of intracystic glucose based on the cut-off threshold for each study.

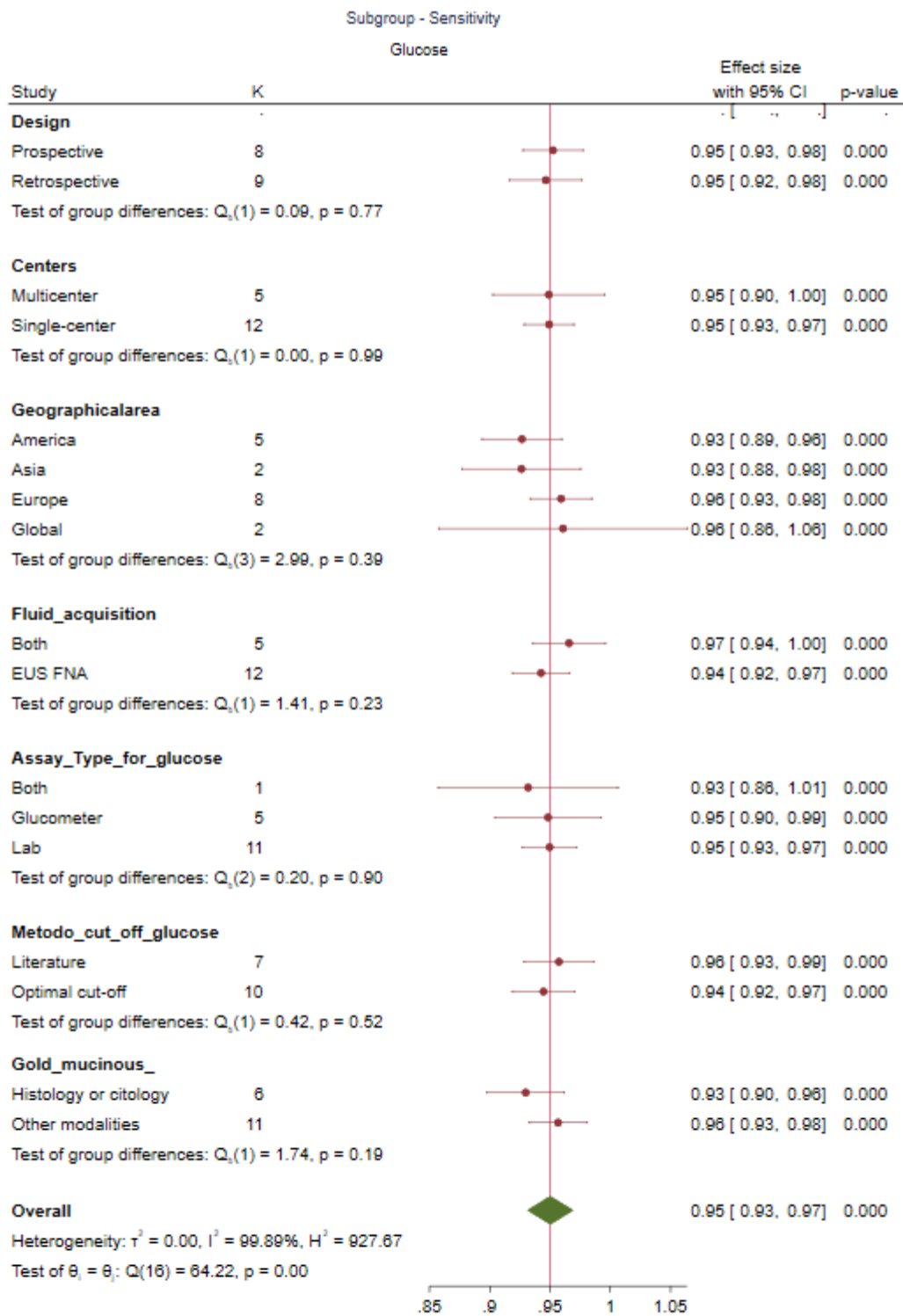


Supplementary Figure 4 Bivariate boxplot for exploring the heterogeneity of the included studies regarding the use of intracystic CEA.

Glucose - accuracy

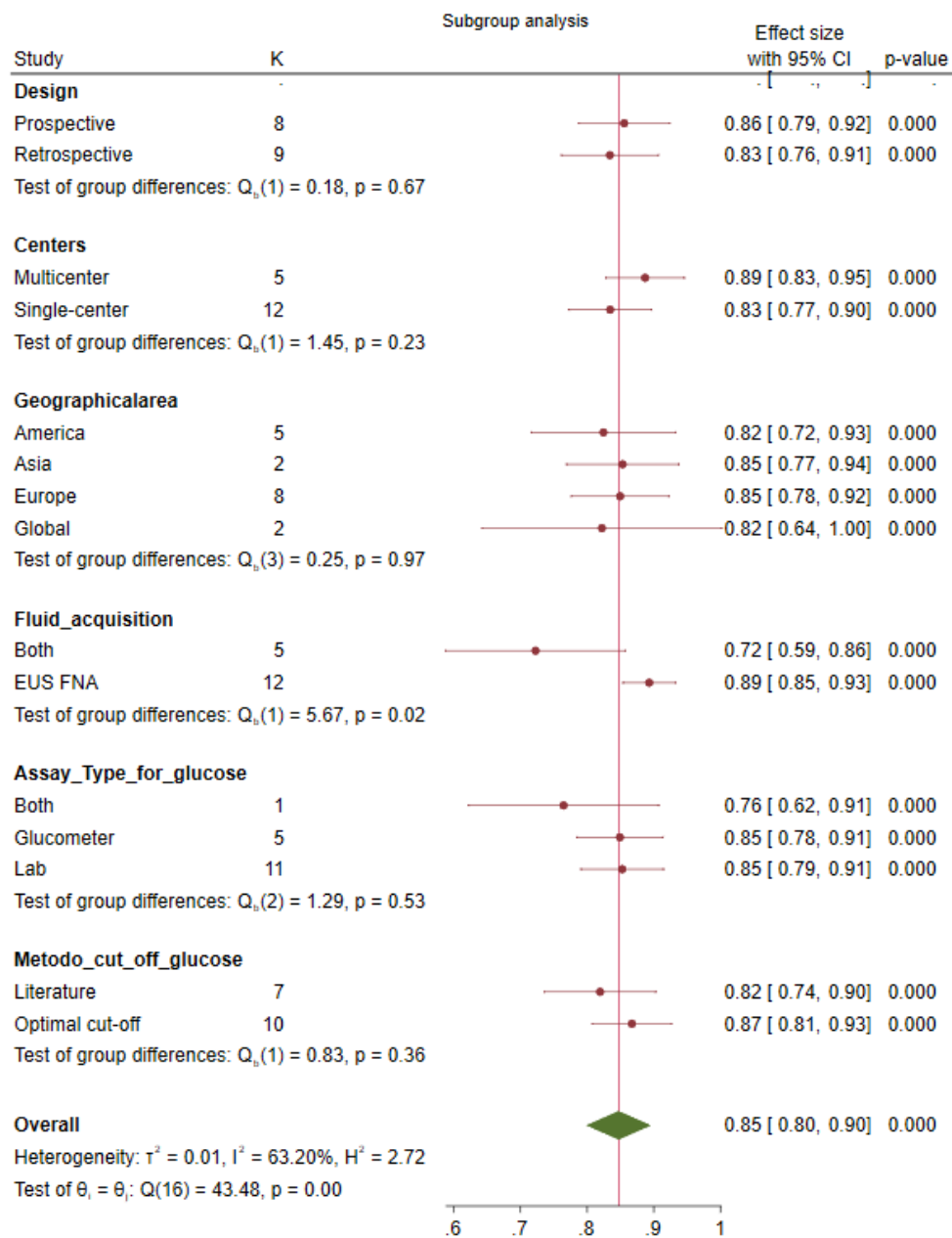


Supplementary Figure 5 Forest plot of subgroup analyses evaluating the pooled accuracy of intracystic glucose for diagnosing mucinous pancreatic cysts.



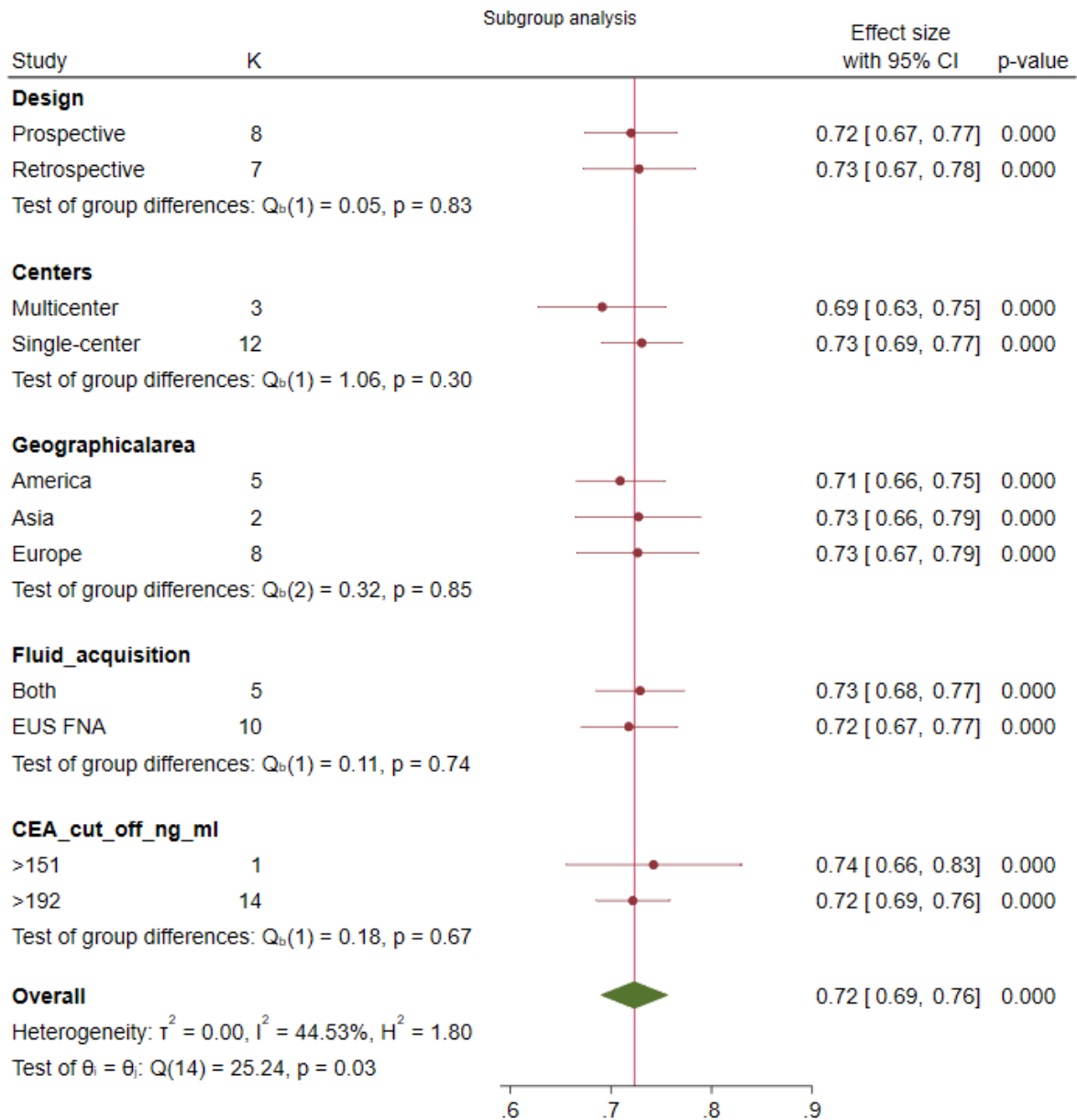
Supplementary Figure 6 Forest plot of subgroup analyses evaluating the pooled sensitivity of intracystic glucose for diagnosing mucinous pancreatic cysts.

Glucose - specificity



Supplementary Figure 7 Forest plot of subgroup analyses evaluating the pooled specificity of intracystic glucose for diagnosing mucinous pancreatic cysts.

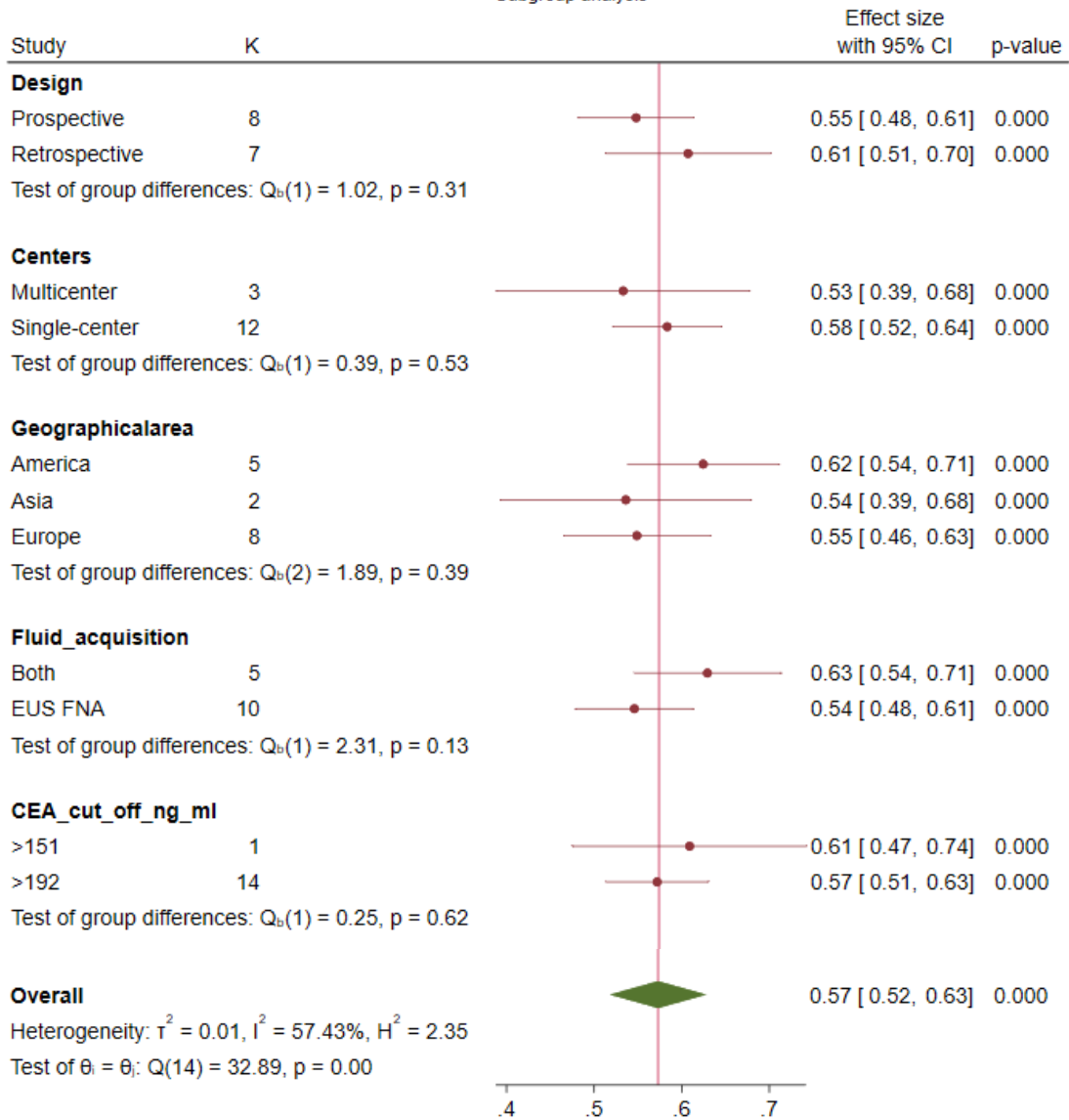
CEA - accuracy



Supplementary Figure 8 Forest plot of subgroup analyses evaluating the pooled accuracy of intracystic CEA for diagnosing mucinous pancreatic cysts.

CEA - sensitivity

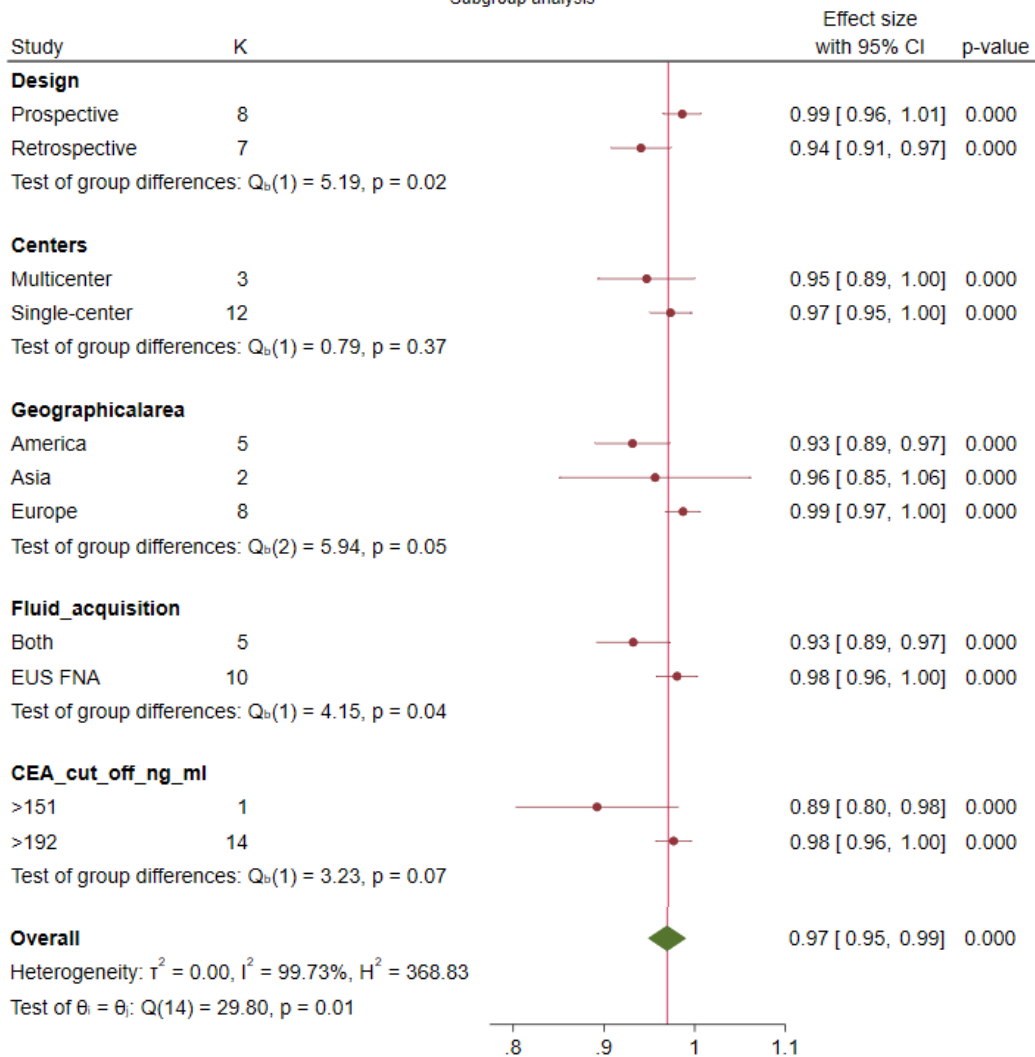
Subgroup analysis



Supplementary Figure 9 Forest plot of subgroup analyses evaluating the pooled sensitivity of intracystic CEA for diagnosing mucinous pancreatic cysts.

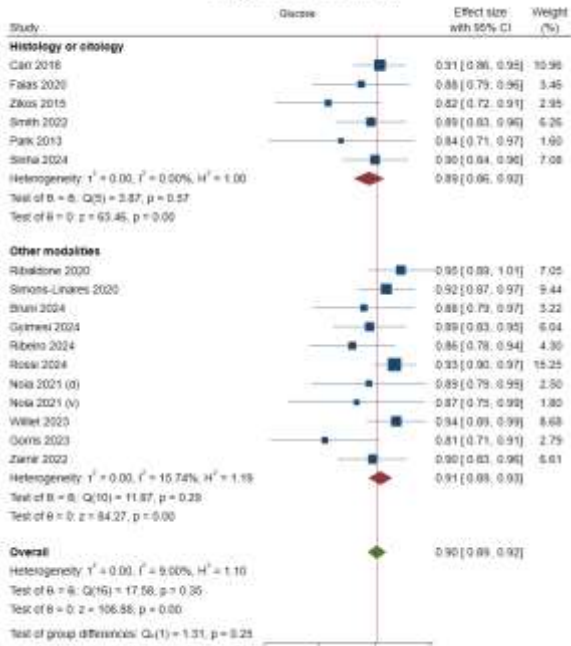
CEA - specificity

Subgroup analysis



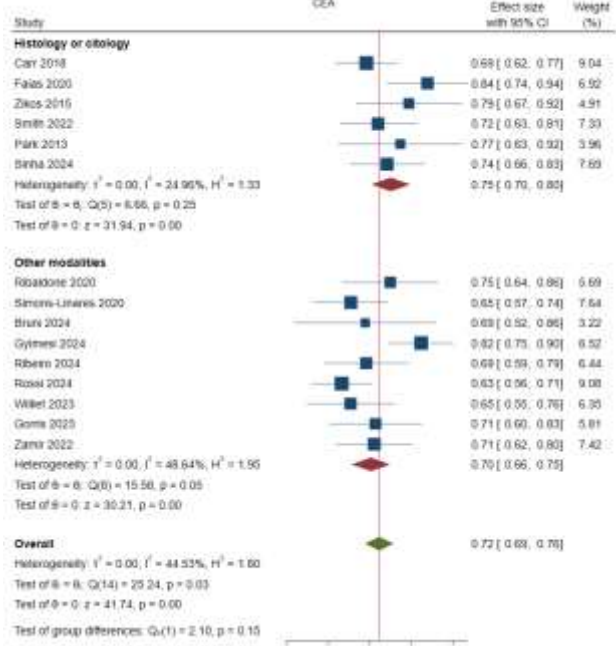
Supplementary Figure 10 Forest plot of subgroup analyses evaluating the pooled specificity of intracystic CEA for diagnosing mucinous pancreatic cysts.

Subgroup - Accuracy



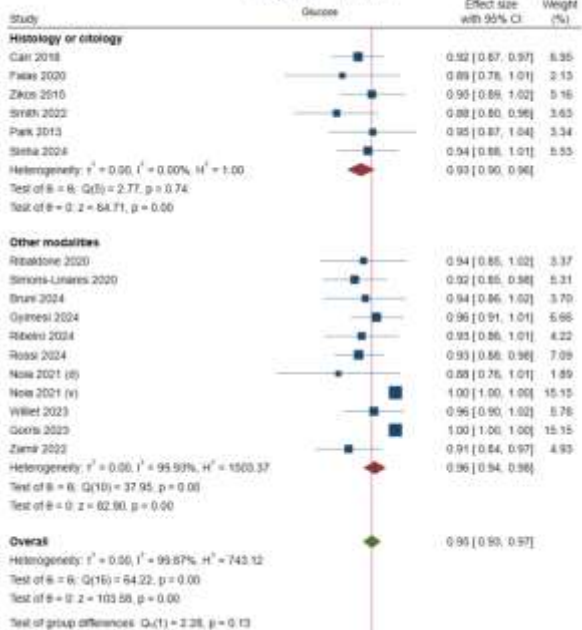
A

Subgroup - Accuracy



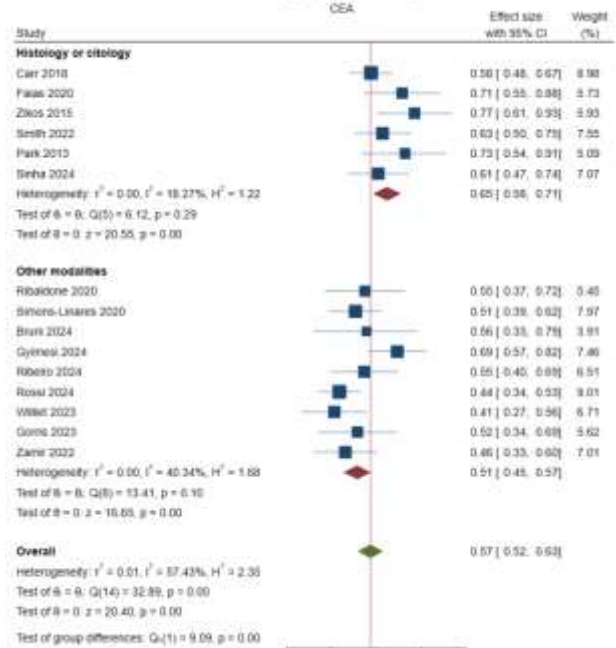
B

Subgroup - Sensitivity

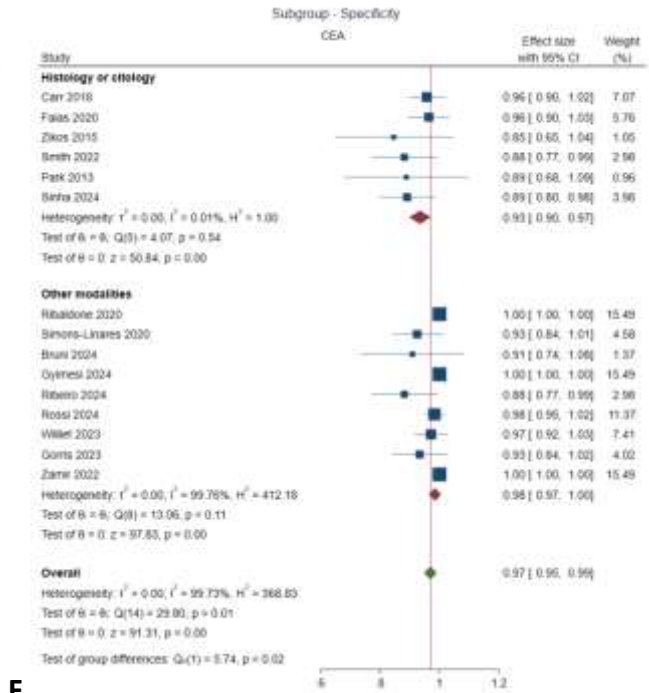
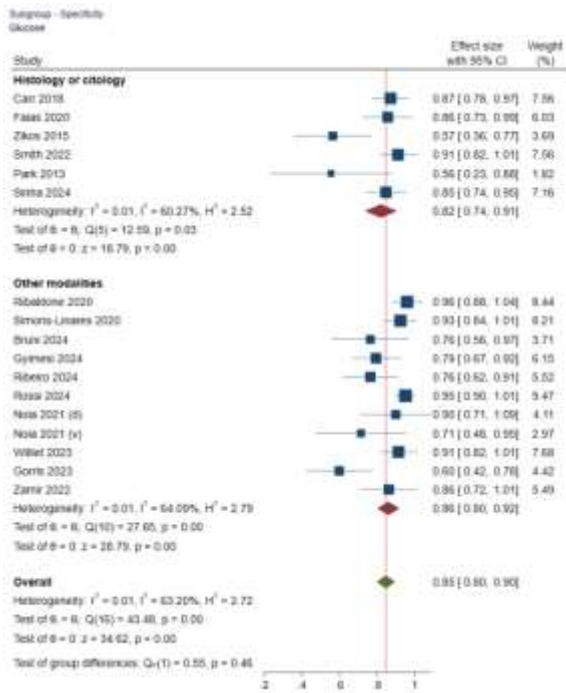


C

Subgroup - Sensitivity



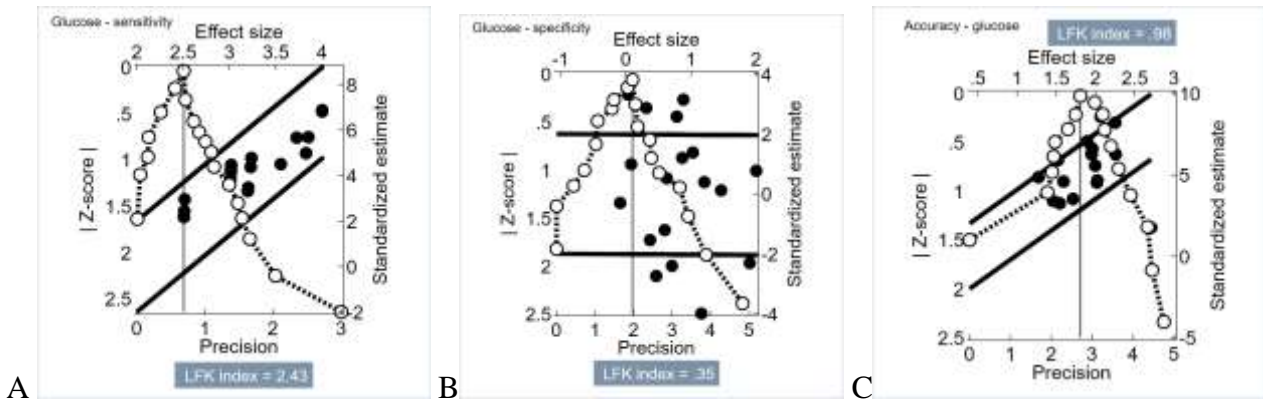
D



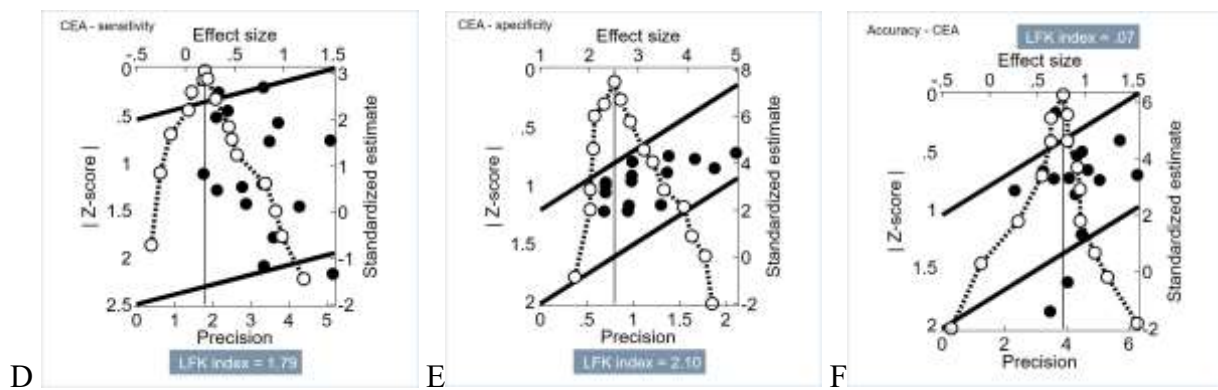
E

F

Supplementary Figure 11 Forest plot of subgroup analyses based on the diagnostic standard for mucinous cysts (surgical samples or cytology vs other modalities) evaluating: A) Accuracy of glucose; B) accuracy of CEA;; D) sensitivity of CEA; E) specificity of glucose; F) specificity of CEA.



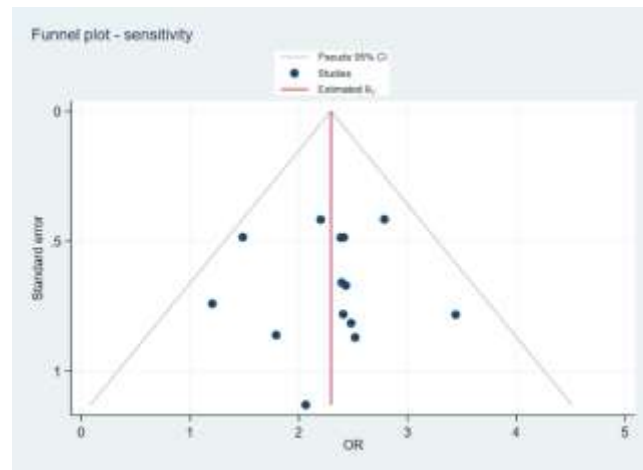
Supplementary Figure 12 Doi plot assessing publication bias for sensitivity (A), specificity (B) and accuracy (C) estimates of glucose.



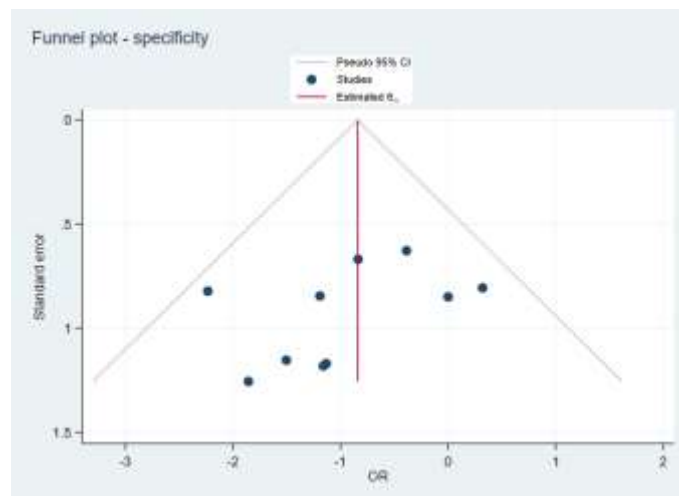
Supplementary Figure 12 Doi plot assessing publication bias for sensibility (D), specificity (E) and accuracy (F) estimates of CEA.



Supplementary Figure 13A. Funnel plot for accuracy while comparing glucose vs CEA showing publication bias



Supplementary Figure 13B. Funnel plot for sensitivity while comparing glucose vs CEA showing no publication bias



Supplementary Figure 13C. Funnel plot for specificity when comparing glucose vs CEA showing no publication bias

Supplementary Table 1. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6,7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 8 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 8 Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9,10 Supplementary Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8,9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8,9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 8,9 Figure 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 9,10 Supplementary Table 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 9,10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-14
	23b	Discuss any limitations of the evidence included in the review.	Page 13
	23c	Discuss any limitations of the review processes used.	Page 13
	23d	Discuss implications of the results for practice, policy, and future research.	Page 11-14
OTHER INFORMATION			

Section and Topic	Item #	Checklist item	Location where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 2 QUADAS-2 Quality Assessment Scale

Study	Risk of bias				Applicability concerns			Overall risk of bias
	Patient selection	Index test	Reference standard	Flow and Timing	Patient selection	Index test	Reference standard	
Carr 2018	★	★★	★	★	★	★	★	Low
Faias 2020	★★	★★	★	★	★	★	★	Low
Ribaldone 2020	★	★★	★★	★	★	★	★	Low
Simons-Linares 2020	★★	★★	★★	?	★	★	★	High
Zikos 2015	★★	★★	★	?	★	★	★	High
Bruni 2024	★★	★★	★★	★	★	★	★	High
Gyimesi 2024	★	★★	★★	★	★	★	★	Low
Ribeiro 2024	★★	★★	★★	?	★	★	★	High
Rossi 2024	★	★★	★★	★	★	★	★	Low
Noia 2021	★★	★★	★	?	★	★	★	High
Smith 2022	★★	★★	★	★	★	★	★	Low
Park 2013	★	★★	★	?	★	★	★	Low
Williet 2023	★	★★	★★	★	★	★	★	Low
Gorris 2023	★	★★	★★	★	★	★	★	Low
Sinha 2024	★	★★	★	★	★	★	★	Low
Zamir 2022	★★	★★	★★	★	★	★	★	High

★= low risk; ★★=High risk; ?=unclear risk.

Supplementary Table 3 Technical findings of the biomarkers

Study	Fluid obtained by	Type of glucose testing	Glucose cut off for mucinous lesions (mg/dL)	CEA cut off for mucinous lesions (mg/dL)
Carr, 2018 (10)	Surgical or EUS FNA	Glucometer	<50	>192
Ribaldone, 2020 (12)	EUS FNA	Laboratory	<50	>192
Simons-Linares, 2020 (13)	EUS FNA	Laboratory	≤41	≥ 192
Bruni, 2024 (17)	EUS FNA	glucometer	<50	>192
Gyimesi, 2024 (18)	EUS FNA	Laboratory	<50	>192
Ribeiro, 2024 (19)	EUS-FNA	Glucometer and Laboratory	<50	>192
Rossi, 2024 (20)	EUS-FNA	Laboratory	≤58	>192
Faias, 2020 (38)	EUS-FNA	Glucometer	<50	>192
Zikos, 2015 (11)	Surgical or EUS FNA	Laboratory	<50	>192
Smith, 2022 (22)	EUS- FNA	Laboratory	<40	>192
Williet, 2023 (23)	EUS- FNA	Laboratory	<41.8	>192
Gorris, 2023 (39)	EUS-FNA	Glucometer and Laboratory	<50	>192
Sinha, 2024 (24)	Surgical or EUS FNA	Laboratory	<50	>151
Zamir, 2022 (40)	EUS-FNA	Laboratory	<87	>192
Noia, 2021 (D) (21)	EUS-FNA	Glucometer	<73	NR
Noia, 2021 (V) (21)	EUS-FNA	Glucometer	<73	NR
Park, 2013 (14)	Surgical or EUS-FNA	Laboratory	<66	>192

EUS-FNA = Endoscopic Ultrasound fine needle aspiration; CEA = Carcinoembryonic Antigen; NR =not reported

Supplementary Table 4 Summaries of subgroup analysis when removing the identified outliers after boxplot bivariate analysis

Test	Diagnostic metric	Subgroup	Pooled effect size, %	CI 95%, %	Tau2	I ² , %
CEA	Sensitivity	Without outliers of boxplot bivariate analysis	58.4	52.3-64.5	0.0072	60.72
	Specificity	Without outliers of boxplot bivariate analysis	95.3	92.6-98	0.0009	59.69
Glucose	Sensitivity	Without outliers of boxplot bivariate analysis	93.3	91.5-95	0.00001	0
	Specificity	Without outliers of boxplot bivariate analysis	86.9	82.5	0.0035	54.44

CEA = Carcinoembryonic antigen; OR= Odds ratio; CI= confidence interval