Supplementary appendix

Table S1 The PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
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.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
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.	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.	5
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.	5
	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.	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.	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.	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)).	6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6-7
	13d	Describe any methods used to synthesize results and provide a rationale	6-7

Section and Topic	Item #	Checklist item	Location where item is reported
		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.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6-7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6-7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6-7
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.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7-8
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.	8-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	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.	8-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10
	23b	Discuss any limitations of the evidence included in the review.	11-12
	23c	Discuss any limitations of the review processes used.	11-12
	23d	Discuss implications of the results for practice, policy, and future research.	11-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	3

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	2
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.	2

Table S2 Search strategy used for the meta-analysis in the PubMed/Medline, Web of Science, and Scopus databases

Database	**Keywords**
Pubmed/Medline	
#1	Search: **Pancreatic[Title/Abstract]** Sort by: **Most Recent** "Pancreatic"[Title/Abstract]
#2	Search: **((((Carcinoma[Title/Abstract]) OR (cancer[Title/Abstract])) OR (neoplasm[Title/Abstract])) OR (tumor[Title/Abstract])) OR (tumour[Title/Abstract])** Sort by: **Most Recent** "Carcinoma"[Title/Abstract] OR "cancer"[Title/Abstract] OR "neoplasm"[Title/Abstract] OR "tumor"[Title/Abstract] OR "tumour"[Title/Abstract]
#3	Search: **(circulating cfDNA[Title/Abstract]) OR (circulating ctDNA[Title/Abstract])** Sort by: **Most Recent** "circulating cfdna"[Title/Abstract] OR (("blood circulation"[MeSH Terms] OR ("blood"[All Fields] AND "circulation"[All Fields]) OR "blood circulation"[All Fields] OR "circulation"[All Fields] OR "circulations"[All Fields] OR "circulate"[All Fields] OR "circulated"[All Fields] OR "circulates"[All Fields] OR "circulating"[All Fields]) AND "ctDNA"[Title/Abstract]) **Translations** **circulating:** "blood circulation"[MeSH Terms] OR ("blood"[All Fields] AND "circulation"[All Fields]) OR "blood circulation"[All Fields] OR "circulation"[All Fields] OR "circulations"[All Fields] OR "circulate"[All Fields] OR "circulated"[All Fields] OR "circulates"[All Fields] OR "circulating"[All Fields]
#4	**#1 AND #2 AND #3** **Search: ((Pancreatic[Title/Abstract]) AND (((((Carcinoma[Title/Abstract]) OR (cancer[Title/Abstract])) OR (neoplasm[Title/Abstract])) OR (tumor[Title/Abstract])) OR**

	(tumour[Title/Abstract]))) **AND** **((circulating cfDNA[Title/Abstract])** **OR** **(circulating ctDNA[Title/Abstract]))** **Sort by: Most Recent** "Pancreatic"[Title/Abstract] AND ("Carcinoma"[Title/Abstract] OR "cancer"[Title/Abstract] OR "neoplasm"[Title/Abstract] OR "tumor"[Title/Abstract] OR "tumour"[Title/Abstract]) AND ("circulating cfdna"[Title/Abstract] OR (("blood circulation"[MeSH Terms] OR ("blood"[All Fields] AND "circulation"[All Fields]) OR "blood circulation"[All Fields] OR "circulation"[All Fields] OR "circulations"[All Fields] OR "circulate"[All Fields] OR "circulated"[All Fields] OR "circulates"[All Fields] OR "circulating"[All Fields]) AND "ctDNA"[Title/Abstract])) Translations circulating: "blood circulation"[MeSH Terms] OR ("blood"[All Fields] AND "circulation"[All Fields]) OR "blood circulation"[All Fields] OR "circulation"[All Fields] OR "circulations"[All Fields] OR "circulate"[All Fields] OR "circulated"[All Fields] OR "circulates"[All Fields] OR "circulating"[All Fields]
Web of Science (WoS)	
#1	TOPIC: (ALL=(Pancreatic)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCIS, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
#2	((((ALL=(Carcinoma)) OR ALL=(cancer)) OR ALL=(neoplasm)) OR ALL=(tumor)) OR ALL=(tumour) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCIS, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
#3	(ALL=(circulating cfDNA)) OR ALL=(circulating ctDNA) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCIS, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#4	#1 AND #2 AND #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCIS, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
Scopus	
#1	pancreatic
#2	carcinoma
#3	cancer
#4	neoplasm
#5	tumor*
#6	tumour*
#7	#2 OR #3 OR #4 OR #5 OR #6
#8	circulating cfDNA
#9	circulating ctDNA
#10	#8 OR #9
#11	#1 AND #7 AND #10

Table S3 The adapted version of the REporting recommendations for tumor MARKer prognostic studies (REMARK) criteria for biomarker studies (McShane et al. 2005)

Adapted REMARK criteria for quality assessment (1 point/criteria)	
1	Case selection adequate (baselines from medical chart)
2	State the marker examined and the aim of the study
3	Reporting at least the following characteristics: location of primary tumor (esophagus, stomach or pancreas), disease stage, histology and received treatment
4	State the time and type of sampling (serum/plasma)
5	State the assay methods used and provide a detailed protocol (at least cfDNA isolation, sequence method and sequence depth)
6	A clear description of the flow of patients through the study
7	A clear description of the reasons of dropout

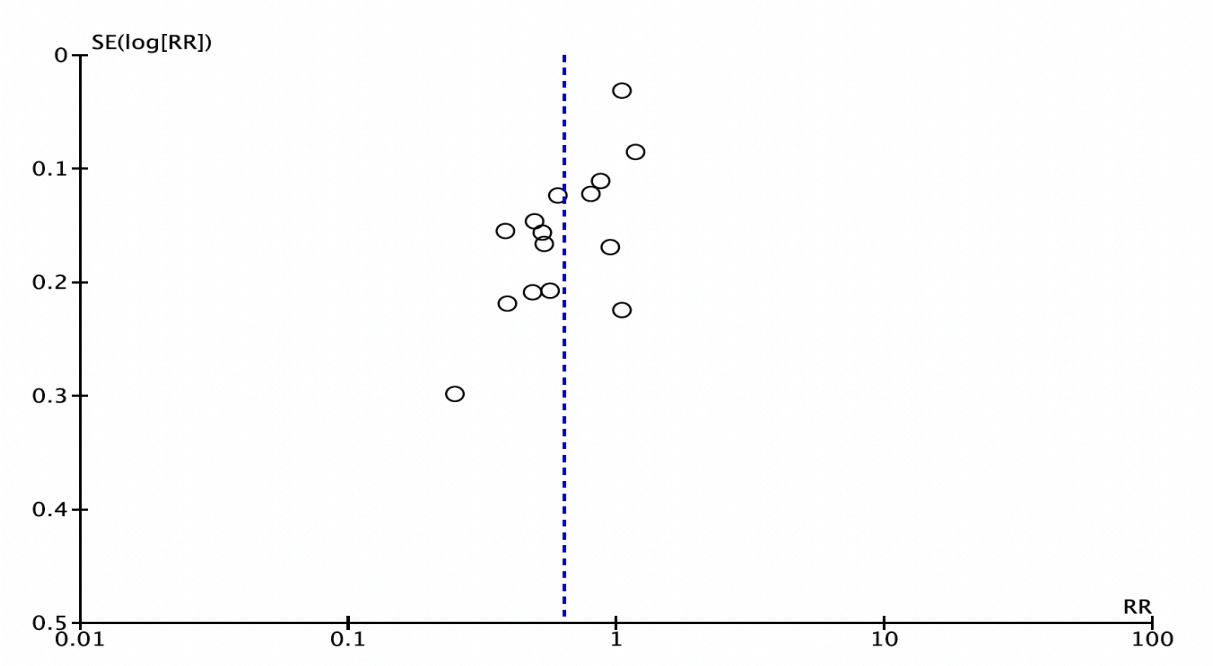

Fig. S1 The funnel plot of the meta-analysis of diagnostic accuracy of ctDNA compared to CA 19.9 in all disease stages of pancreatic cancer is approximately symmetrical and, in accordance with the results of Egger's ($p > .05$) and Begg's ($p > .05$) tests, fades the possibility of potential publication bias

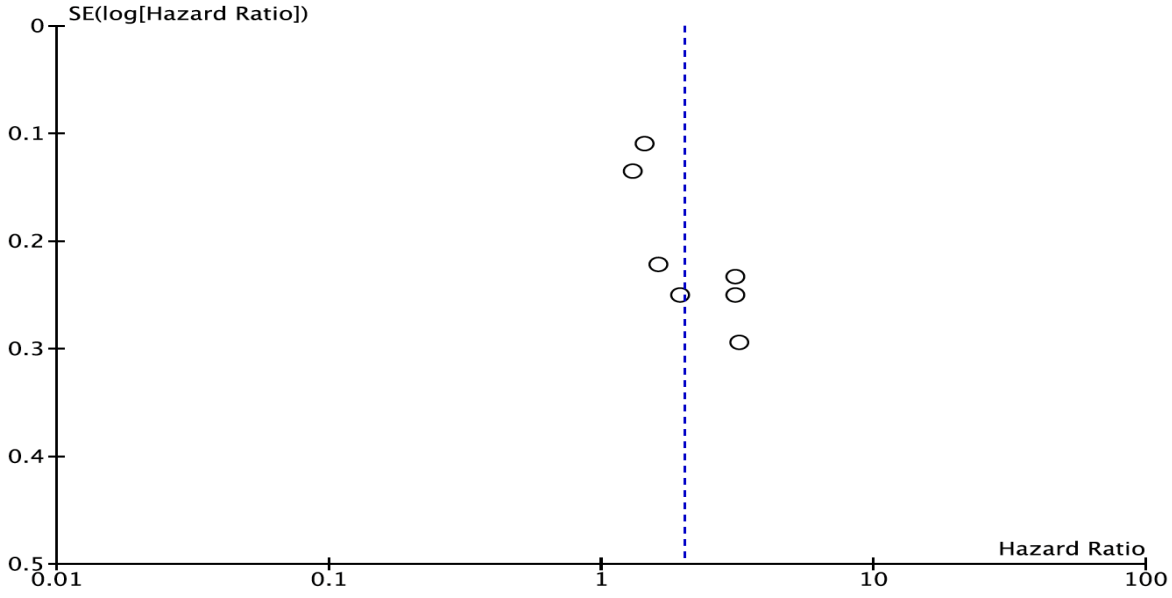

Fig. S2 The funnel plot of the meta-analysis of ctDNA in terms of the prognostic role on overall survival is approximately symmetrical and, in accordance with the results of Egger's ($P > .05$) and Begg's ($P > .05$) tests, fades the possibility of potential publication bias

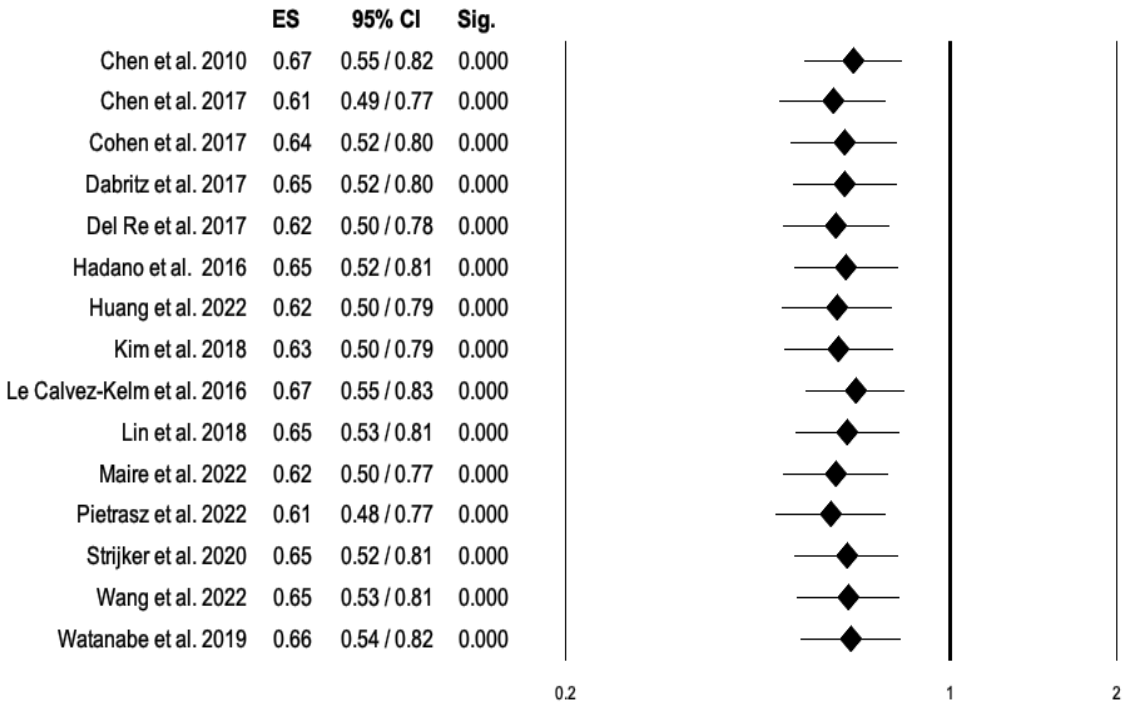

Fig. S3 Sensivity analyses of diagnostic accuracy of ctDNA/cfDNA compared to CA 19.9 in all disease stages of pancreatic cancer (ES = Risk raito; Sig = Statistical significance)

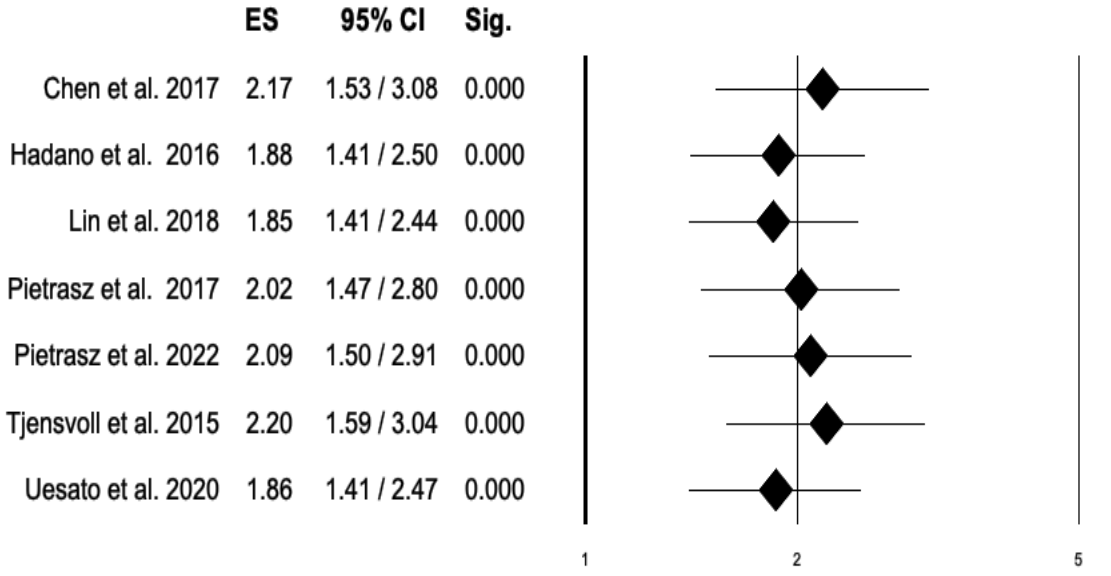

Fig. S4 Sensivity analysis of ctDNA in terms of its prognostic role in overall survival (ES = Risk raito; Sig = Statistical significance)

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