Title

Persistently High Procalcitonin and C-Reactive Protein are Good Predictors of Infection in Acute Necrotizing Pancreatitis: A Systematic Review and Meta-Analysis

Authors

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Document S1: 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.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7
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.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	7
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.	7
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.	7
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.	7
	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.	7
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.	7
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.	8
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)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	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.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8

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

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

For more information, visit: http://www.prisma-statement.org/

Document S2: Search key

acute AND pancrea* AND necro* AND infect*

Document S3: Exclusion criteria during the full text selection

The studies that compared severe AP and IPN were excluded. [1-107] Moreover, 48 articles were not included in the analysis because they did not contain any relevant data related to laboratory parameters. [61–107].

Table S1: Tabular display of risk of bias assessment with QUADAS-2 and QUADAS-C tools

Study	Test	Risk of bias (QUADAS-2)				Applicability concerns (QUADAS-2)		
		P	I	R	FT	P	I	R
Brand M, 2014		✓	✓	✓	✓	✓	✓	✓
Mándi Y, 2000		✓	✓	✓	✓	✓	✓	✓
Chen HZ, 2017		✓	✓	✓	✓	✓	✓	✓
Wiese ML, 2022		✓	✓	✓	✓	✓	✓	✓
Riché FC, 2003		✓	✓	✓	✓	✓	✓	✓
Ueda T, 2007		✓	✓	?	?	✓	✓	✓
Rotar O, 2022		✓	✓	?	✓	✓	✓	✓
Müller CA, 1999		✓	✓	✓	?	✓	✓	✓
Block S, 1987		?	✓	✓	?	✓	✓	✓
Rotar O, 2019		✓	✓	✓	✓	✓	✓	✓
Dambrauskas Z, 2007		✓	✓	✓	?	✓	✓	✓
Rau B, 2000		✓	✓	✓	?	✓	✓	✓
Zheng L, 2011		✓	✓	✓	?	✓	✓	✓

P = patient selection; I = index test; R = reference standard; FT = flow and timing,
✓ indicates low risk; ✗ indicates high risk; ? indicates unclear risk.

Table S2: Summary of evidence tables (GRADE approach)

a)

Question: Should CRP be used to diagnose INP in NP in the early phase ANP in the early phase ?

Sensitivity	0.45 to 0.65
Specificity	0.73 to 0.89

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	
True positives (patients with INP)	5 studies 204 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	0 to 0	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having INP)								0 to 0	
True negatives (patients without INP)	5 studies 277 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	727 to 891	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having INP)								109 to 273	

Explanations

a. Confidence intervals are wide

b)

Question: Should PCT be used to diagnose INP in ANP in the early phase ?

Sensitivity	0.61 to 0.78
Specificity	0.58 to 0.75

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	
True positives (patients with INP)	3 studies 120 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	0 to 0	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having INP)								0 to 0	
True negatives (patients without INP)	3 studies 173 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	583 to 750	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having INP)								250 to 417	

Explanations

a. confidence intervals are wide

c)

Question: Should CRP be used to diagnose INP in ANP in the late phase ?

Sensitivity	0.83 to 0.92
Specificity	0.70 to 0.81

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	
True positives (patients with INP)	3 studies 58 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	0 to 0	⊕⊕○○ Low
False negatives (patients incorrectly classified as not having INP)								0 to 0	
True negatives (patients without INP)	3 studies 68 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	700 to 815	⊕⊕○○ Low
False positives (patients incorrectly classified as having INP)								185 to 300	

Explanations

a. Confidence intervals are wide

d)

Question: Should PCT be used to diagnose INP in ANP in the late phase ?

Sensitivity	0.75 to 0.92
Specificity	0.61 to 0.88

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	
True positives (patients with IPN)	3 studies 95 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	0 to 0	⊕⊕○○ Low
False negatives (patients incorrectly classified as not having IPN)								0 to 0	
True negatives (patients without IPN)	3 studies 130 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	612 to 880	⊕⊕○○ Low
False positives (patients incorrectly classified as having IPN)								120 to 388	

Explanations

a. confidence intervals are wide

e)

Question: Should WBC be used to diagnose INP in ANP in the early phase ?

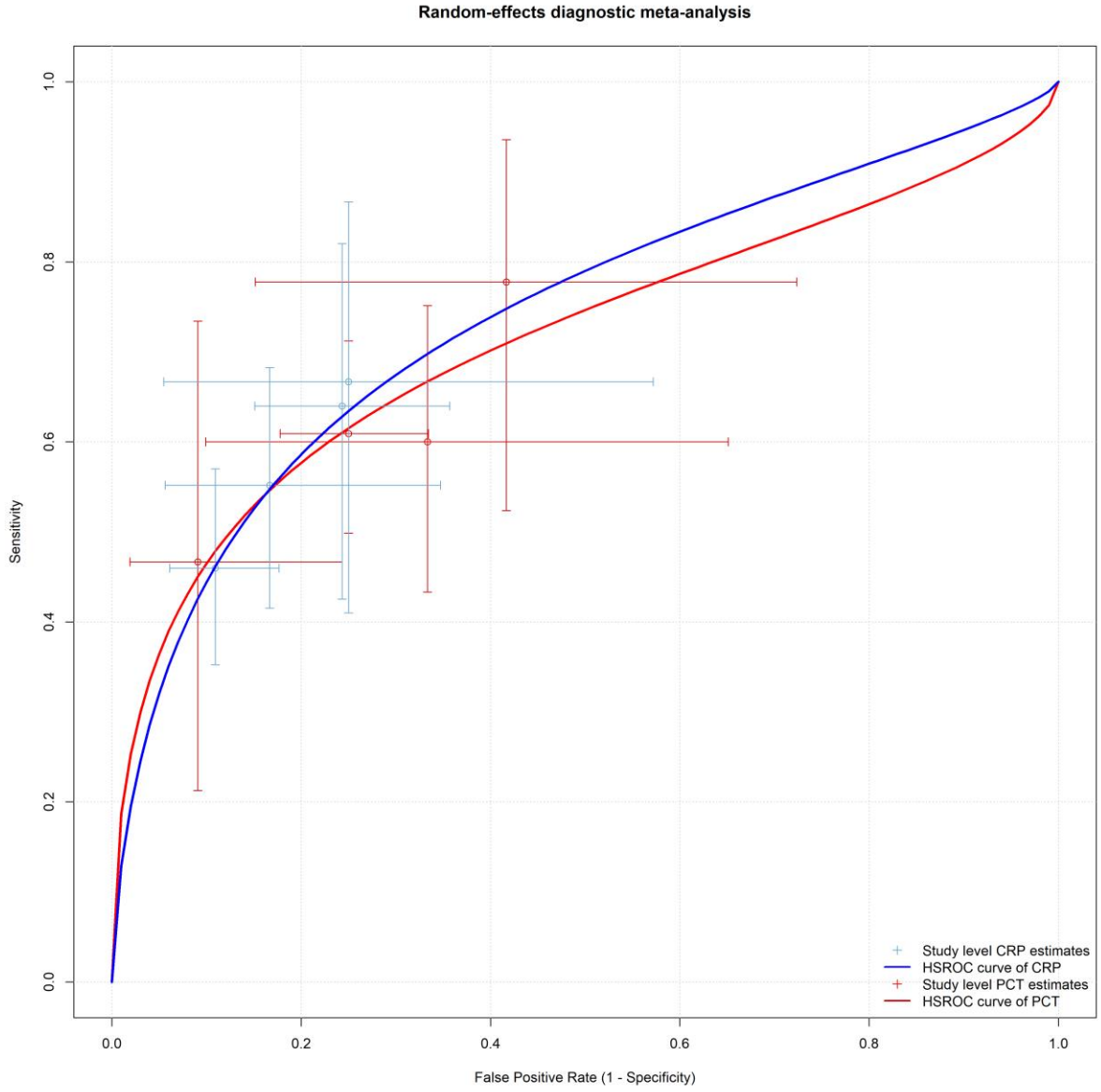
Sensitivity	0.57 to 0.58
Specificity	0.62 to 0.80

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	
True positives (patients with INP)	3 studies 171 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	0 to 0	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having INP)								0 to 0	
True negatives (patients without INP)	3 studies 232 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious[a]	none	620 to 800	⊕⊕◯◯ Low
False positives (patients incorrectly classified as having INP)								200 to 380	

Explanations

a. a.Confidence intervals are wide

Figure S1: ROC plot visualizing the diagnostic performance of PCT and CRP levels [28,29,30,31,36].



CRP: C-reactive protein

PCT: procalcitonin

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