The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: Systematic review

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Background. *Many studies have evaluated serum levels of procalcitonin (PCT) as a predictor in the development of severe acute pancreatitis (SAP) and infected pancreatic necrosis (IPN). This study assesses the value of PCT as a marker of development of SAP and IPN.*
Methods. *Medline, Web of Science, the Cochrane clinical trials register, and international conference proceedings were searched systematically for prospective studies, which evaluated the usefulness of PCT as a marker of SAP and IPN. The sensitivity, specificity, and diagnostic odds ratios (DORs) were calculated for each study, and the study quality and heterogeneity among the studies were evaluated.*
Results. *Twenty-four of 59 studies identified were included in data extraction. The sensitivity and specificity of PCT for development of SAP were 0.72 and 0.86, respectively (area under the curve [AUC] = 0.87; DOR = 14.9; 95% confidence interval [CI] = 5.6–39.8), albeit with a significant degree of heterogeneity (Q = 28.56, P < .01). The sensitivity and specificity of PCT for prediction of infected pancreatic necrosis were 0.80 and 0.91 (AUC = 0.91; DOR = 28.3; 95% CI = 13.8–58.3) with no significant heterogeneity (Q = 7.83, P = .18). No significant heterogeneity was observed among the studies when only higher quality studies (AUC = 0.91; DOR = 30.7; 95% CI = 10.7–87.8) or studies that used a cutoff PCT level >0.5 ng/mL (AUC = 0.88, 32.8; 95% CI = 10.1–106.6) were included.*
Conclusion. *Serum measurements of PCT may be valuable in predicting the severity of acute pancreatitis and the risk of developing infected pancreatic necrosis. (Surgery 2009;146:72-81.)*

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ACUTE PANCREATITIS has a range of presentations, from a mild self-limiting disease to a severe attack, which can result in the development of local and systemic complications that carry a significant risk of mortality.[1-4] The progression to severe pancreatitis is associated with the inappropriate activation of an inflammatory cascade that leads to the development of a systemic inflammatory response syndrome (SIRS).[5-8] This inflammatory cascade in turn may result in the development of multiorgan dysfunction syndrome (MODS) and, in a proportion of patients, death from acute pancreatitis. Persistent SIRS is associated with MODS and death, and as a result, persistent SIRS is an early indicator of the likely severity of acute pancreatitis.[9,10]

Procalcitonin (PCT) is the inactive propeptide of the hormone calcitonin, which is involved in calcium homeostasis.[11,12] It is released by hepatocytes and peripheral monocytes as well as by C-cells of the thyroid gland. In the C-cells of the thyroid gland, procalcitonin is cleaved into the biologically active forms of the hormone, calcitonin and katacalcin, which is a protein residue.[11-18] The increased serum PCT correlates closely with the inflammatory response of a host to microbial infections.[11,12] In patients who suffer from acute pancreatitis, PCT has been shown to predict the development of infected pancreatic necrosis.[13,14] In addition, PCT has been found to be an early predictor of severity[15-17] and organ failure[18-21] in patients with acute pancreatitis.

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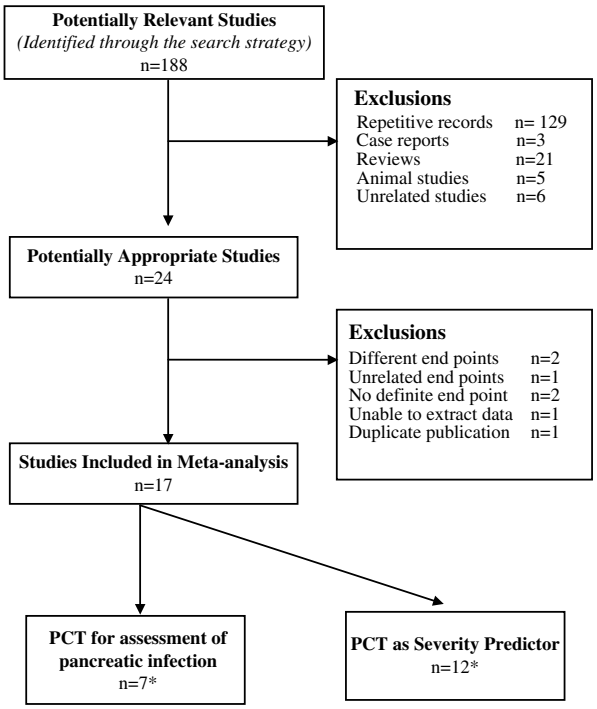

Fig 1. The QUORUM chart illustrating the process of identification of relevant studies. *Two studies were included in both groups as they examined PCT as a severity predictor and as a predictor of development of infected pancreatic necrosis as 2 separate end points.[13]

Two previous attempts have been made to assess the value of procalcitonin as a predictor of severity of acute pancreatitis through the use of systematic reviews but with contradictory results.[20,22] Shafiq et al[22] reported that PCT is not a good predictor of severity of acute pancreatitis; this meta-analysis only included 4 studies and was not a comprehensive review of the literature. A more recent systematic review of the literature reported that PCT has a moderate sensitivity and high specificity at predicting the severity of acute pancreatitis.[20] Subsequent to these publications, many studies, which include a recently published multicenter observational study, have evaluated the role of PCT.[20,23-27]

The aims of our meta-analysis were to assess the value of procalcitonin in predicting the severity of acute pancreatitis and the development of infected pancreatic necrosis.

METHODS

Search strategy and study selection. A literature search was conducted using Medline, Web of Science, Embase, and the Cochrane Library for all clinical papers published between January 1966 and April 2008 that evaluated the value of serum PCT as a predictor of severity of acute pancreatitis or as a predictor of the development of infected pancreatic necrosis. More publications were identified using the "related article" function in PubMed. No language restrictions were applied during the search. References cited in the identified articles were searched for additional studies. The following keywords were used: "acute pancreatitis" and/or "severe acute pancreatitis" and/or "infected pancreatic necrosis," combined with "procalcitonin" and/or "calcitonin." All abstracts from major gastrointestinal meetings from January 1990 to April 2008 were searched manually. No formal inquiry was made through pharmaceutical companies or research funding bodies for unpublished trials.

Data extraction. Three reviewers (R.M., S.A.S., and P.V.P.) searched the literature independently as well as reviewed and extracted the data from each study. All data collection were performed according to a prespecified protocol with the following information being extracted from each study: first author, year of publication, population characteristics, study design, inclusion and exclusion criteria, and number of subjects, as well as the method of determination of severity of acute pancreatitis. All discrepancies were resolved by consensus among authors.

Inclusion criteria. All studies that reported data on patients with a confirmed diagnosis of acute pancreatitis and that compared the measurement of serum PCT with other validated severity stratification methods were included. Studies without any form of severity stratification were excluded. An attempt was made to contact the corresponding author of the studies that otherwise met the inclusion criteria, but the data required were not directly extractable or calculable from the published manuscripts.

Exclusion criteria. Noncomparative studies were excluded, which included review articles and case reports, as well as all animal studies. Within the studies evaluated, those with endpoints that were not comparable or from which it was impossible to calculate these endpoints from the published results were excluded. Studies that displayed a "zero cell" for the outcomes of interest in both groups were excluded.

Outcomes of interest and definitions. The primary end points were sensitivity, specificity, positive and negative predictive values of PCT as a predictor of severity of acute pancreatitis, as well as the sensitivity, specificity, and positive and negative predictive values of PCT at predicting the development of infected pancreatic necrosis.

The definition of severe acute pancreatitis (SAP) was based on the Atlanta classification[28] as

Table I. Technical characteristics of the included studies

Study (year)	*Study design*	*Evaluation*	*Time of blood samples*	*Method of PCT measurement*	*Time(s) of evaluation*	*Cutoff values for PCT (ng/mL)*
Rau et al[13] (1997)	Prospective	Mild vs SAP	Daily for 14 days	BRAHMS-IA	Highest value	1.8
Bertsch et al[37] (1997)	Prospective	Sterile vs IPN	Daily for 3 days	RIA	Highest value	0.5
Müller et al[33] (2000)	Prospective	Sterile vs IPN	Daily for 14 days	BRAHMS-IA	Highest value	0.48
Mandi et al[14] (2000)	Prospective	Mild vs SAP	Daily for 14 days	BRAHMS-IA	48 h	1.2
Pindak et al[38] (2000)	Prospective	Mild vs SAP	Admission+ day 1	BRAHMS-IA	Highest value	0.5
Pezzilli et al[34] (2000)	Prospective	Mild vs SAP	Daily for 5 days	BRAHMS-IA	—	0.25
Melzi D'Eril et al[35] (2000)	Prospective	Mild vs SAP	Day 1	BRAHMS-IA	Day 1	0.5
Frasquet et al[36] (2000)	Prospective	Mild vs SAP	Day 1	PCT-Q	Day 1	0.5
Kylanpaa-Back et al[18] (2001)	Prospective	Mild vs SAP	Day 1	BRAHMS-IA	Day 1	0.4
Kylanpaa-Back et al[19] (2001)	Prospective	Mild vs SAP	Daily for 2 days	PCT-Q	Day 1	0.5
Riche et al[15] (2003)	Prospective	Sterile vs IPN	Daily for 5 days	BRAHMS-IA	Highest value	2
Pinkola and Darvas[27] (2003)	Prospective	Sterile vs IPN	—	RIA	—	—
Ammori et al[17] (2003)	Prospective	Mild vs SAP	Admission	BRAHMS-IA	Admission	0.5
Olah et al[16] (2005)	Prospective	Sterile vs IPN	Daily for 3 days	PCT-Q	Highest value	0.5
Modrau et al[23] (2005)	Prospective	Mild vs SAP	Daily for 2 days	BRAHMS-IA	Admission +48 h	0.5-0.7
Bulbüller et al[26] (2006)	Prospective	Mild vs SAP	Daily for 14 days	BRAHMS-IA	48 h	0.5
Rau et al[20] (2007)	Prospective	Sterile vs IPN	Daily for 14 days	BRAHMS-IA	Highest value	3.5

BRAHMS-IA, BRAHMS immuno-luminometric assay; *IPN*, infected pancreatic necrosis; *PCT-Q*, procalcitonin strip test; *RIA*, radio immuno assay.

the presence of pancreatic necrosis or development of organ dysfunction, whereas infected pancreatic necrosis was defined either by positive fine-needle aspiration (FNA) culture or by intraoperative findings. These values were either quoted directly in the studies or extractable from the analysis of available values such as true positives, true negatives, false positives, and false negatives.

Statistical analysis. A meta-analysis was performed according to the recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines.[29,30] Pooled sensitivity, specificity, as well as negative and positive predictive values with 95% confidence intervals (95% CI) were estimated, and summary receiver operator characteristic (ROC) curves were constructed to illustrate the performance of PCT as a predictor of severity using the area under the curve (AUC) value. In addition, diagnostic odds ratios with 95% CI were used to quantify the performance of PCT as a predictor of SAP and development of infected pancreatic necrosis.

The quality of each study was assessed independently by each reviewer using the Standards for Reporting of Diagnostic Accuracy (STARD) initiative guidelines.[31] This 25-point score is given to different sections of the study. The results of the STARD analysis were used in a metaregression to assess the effect of the study quality on the diagnostic accuracy of procalcitonin.[31] Disagreements were resolved by consensus. Interobserver agreement was calculated using κ statistics.

To assess heterogeneity, a quantitative sensitivity analysis[32] was undertaken for the following subgroups: study size more than 50 patients, year of publication later than 2001, higher quality studies with a STARD score of 16 or greater, the timing of sample, cutoff value of PCT used, and whether the outcome of interest was the development of SAP or infected pancreatic necrosis.

Most of the statistical analysis was performed using SPSS version 14 software (SPSS, Chicago, IL). Forest plots and summary receiver operator characteristic (SROC) curves were produced using Meta-DiSc version 1.4 statistical software (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain). A P value of less than .05 was considered significant.

RESULTS

Using the aforementioned search strategy, 59 publications (excluding duplicate records) were identified, of which 35 publications were excluded because they were either noncomparative in nature (review articles, case reports, and letters), animal studies, or unrelated studies. In all, 24 studies were

Table II. Demographics of the patients who participated in the studies which were included in this meta-analysis

Study (year)	n	*Country of origin*	*Age (years) median (range)/mean (SD)*	*Male/female*	*Etiology of pancreatitis*
Rau et al[13] (1997)	50	Germany	53 (14–87)	30/20	Biliary: 38%, alcohol: 44%, idiopathic: 18%
Bertsch et al[37] (1997)		Germany			
Müller et al[33] (2000)	64	Switzerland	56.3 (27–87)	39/25	Biliary: 27%, alcohol: 59%, other: 15%
Mandi et al[14] (2000)	20	Slovakia	45.5 (18.2)	14/6	—
Pindak et al[38] (2000)	101	Hungary	—	—	—
Pezzilli et al[34] (2000)	31		66 (34–87)	17/14	Biliary: 81%, other: 19%
Melzi D'Eril et al[35] (2000)	31	Spain	66.4 (34–87)	14/17	Biliary: 80%, alcohol: 20%
Kylänpää-Back et al[18] (2001)	57	Finland	52 (22–82)	41/16	Biliary: 25%, alcohol: 63%, other: 12%
Kylänpää-Back et al[19] (2001)	162	Finland	47(22–97)	107/55	Biliary: 26%, alcohol: 54%: idiopathic: 16%, other 4%
Riche et al[15] (2003)	48	France	53 (24–91)	34/14	Biliary: 81%, other: 19%
Frasquet et al[36] (2003)	51	Spain	59·4 (16·1)	25/26	Biliary: 60%, alcohol: 6% idiopathic 25%, other: 8%
Pinkola et al[27] (2003)	24	Hungary	—	—	—
Ammori et al[17] (2003)	69	United Kingdom	59 (17–92)	38/31	Biliary: 59%, alcohol: 16%, ERCP: 12%, idiopathic: 6%, other: 7%
Olah et al[16] (2005)	24		49 (28–87)	18/6	
Modrau et al[23] (2005)	75	Denmark	57 (18–86)	36/39	Biliary: 56%, alcohol: 16%, idiopathic 17%, other: 11%
Bülbüller et al[26] (2006)	65	Turkey	55.3 (23–85)	32/33	Biliary: 71%, other: 29%
Rau (2007)[27]	104	Europe (multicenter)	50 (19–91)	73/31	Biliary: 27%, alcohol: 59%, other: 15%

ERCP, Endoscopic retrograde cholangiopancreatography; *SD*, standard deviation.

used for comprehensive evaluation.[13-20,23-27,33-45] Of these, 6 studies were excluded from additional analyses[39-44] either because they had no extractable end points or had different end points ($n = 5$),[39-43] or because a temporal overlap existed with respect to patient recruitment with another study by the same author that was included in the analysis ($n = 1$).[44] The remaining 17 studies were stratified into 2 groups based on whether PCT was evaluated as a predictor of SAP ($n = 12$) or as a predictor of development of infected pancreatic necrosis ($n = 7$). Two studies were included in both groups because they evaluated PCT as a predictor of development of infected pancreatitis and the development of multiorgan dysfunction as 2 separate end points.[13,20] The process of identifying eligible articles is illustrated in Fig 1. Overall, 1,001 patients were included in the analysis. In all, 826 patients were involved in the assessment of PCT as a predictor of severity of acute pancreatitis, and 329 were included in the evaluation of PCT as a predictor of development of infected pancreatic necrosis (this approach includes 152 patients who were included in both meta-analyses). Table I describes the technical characteristics of the included studies, whereas Table II describes the demographics of the patient population.

The pooled sensitivity and specificity of serum PCT as predictor of development of SAP were 0.72 (95% CI = 0.64–0.77) and 0.86 (95% CI = 0.83–0.89), respectively, with an overall AUC value of 0.865 (Figs 2 and 3). A significant degree of heterogeneity was observed among the studies that analyzed this outcome measure ($Q = 28.56$; $P < .01$). When the analysis was limited to the studies (n = 8) that had used PCT cutoff values greater than 0.5 ng/mL as a discriminator, a modest increase was observed in the pooled sensitivity (0.73; 95% CI = 0.65–0.80) and specificity (0.87; 95% CI = 0.83–0.92), as well as an increase in the overall AUC (0.88). In addition, no significant heterogeneity was found among the studies ($Q = 7.83$, $P = .18$).

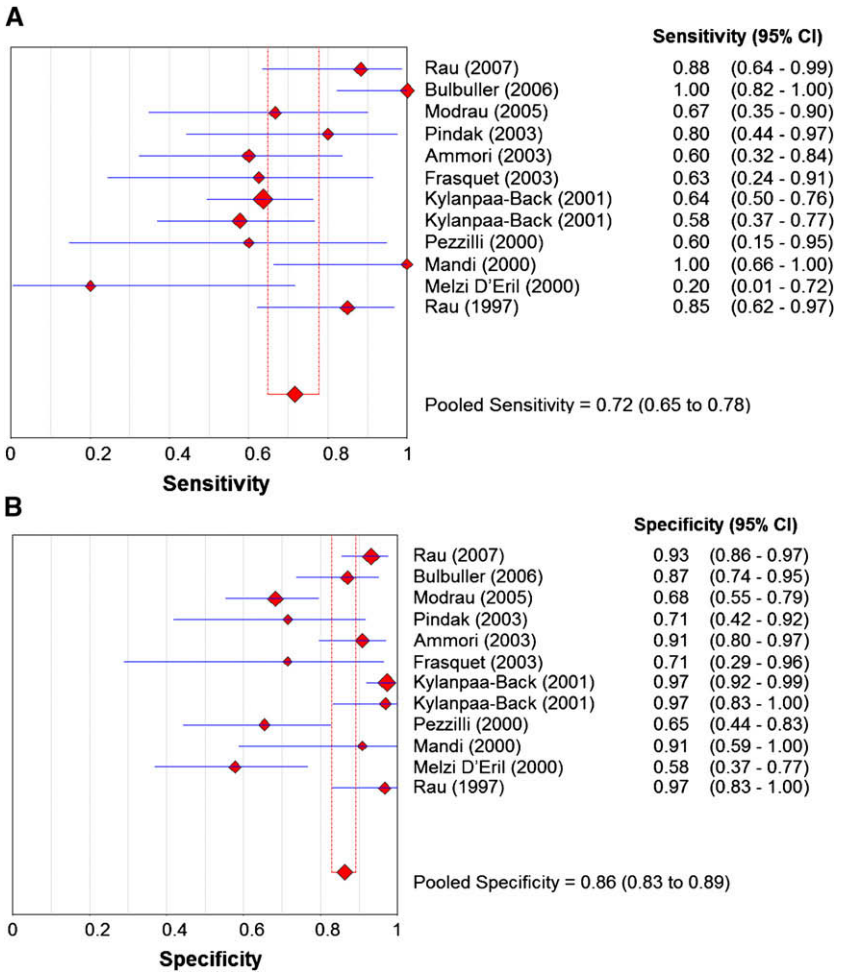

Fig 2. Pooled sensitivity (*A*) and specificity (*B*) of PCT as a predictor of development of SAP.

The pooled sensitivity and specificity of PCT as a predictor of development of infected pancreatic necrosis were 0.80 (95% CI = 0.70–0.87) and 0.91 (95% CI = 0.87–0.94), respectively, with an overall AUC of 0.91 (Figs 4 and 5). No significant heterogeneity was found among the 7 studies that were evaluated in this group ($Q = 5.00$, $P = .54$). Figure 6 illustrates diagnostic odds ratios of PCT as a predictor of the development of SAP (*A*) and infected pancreatic necrosis (*B*).

All the studies that were included in this review were prospective in design and of reasonable quality. The interobserver rating agreement of STARD items was high (0.83 agreement, $\kappa = 0.79$). The median (range) STARD score was 18 (11–24), and of the 17 studies assessed using the STARD checklist, 10 attained a quality score of 16 or greater. Among the 12 studies that evaluated PCT as a predictor of development of SAP, 8 had a quality score of greater than 16. A subgroup analysis of these studies revealed a pooled sensitivity of 0.73 (95% CI = 0.66–0.80), pooled specificity of 0.90 (95% CI: 0.87–0.93), and an AUC of 0.91. No significant heterogeneity was found among these 8 studies ($Q = 3.85$, $P = .26$).

Table III shows the results of the sensitivity analysis for PCT as a predictor of development of SAP or infected pancreatic necrosis. Although the heterogeneity among studies was decreased, it remained significant for studies with a patient population of greater than 50, studies that were published after 2001, and studies in which PCT measurement for prediction of severity was performed within the first 24 h.

DISCUSSION

For over a decade, serum PCT has been available as a predictor of development of SAP, and this meta-analysis confirms that it is reasonably accurate at predicting the development of SAP. All the studies included in this meta-analysis were prospective in nature and of good quality. However, a significant degree of heterogeneity was found

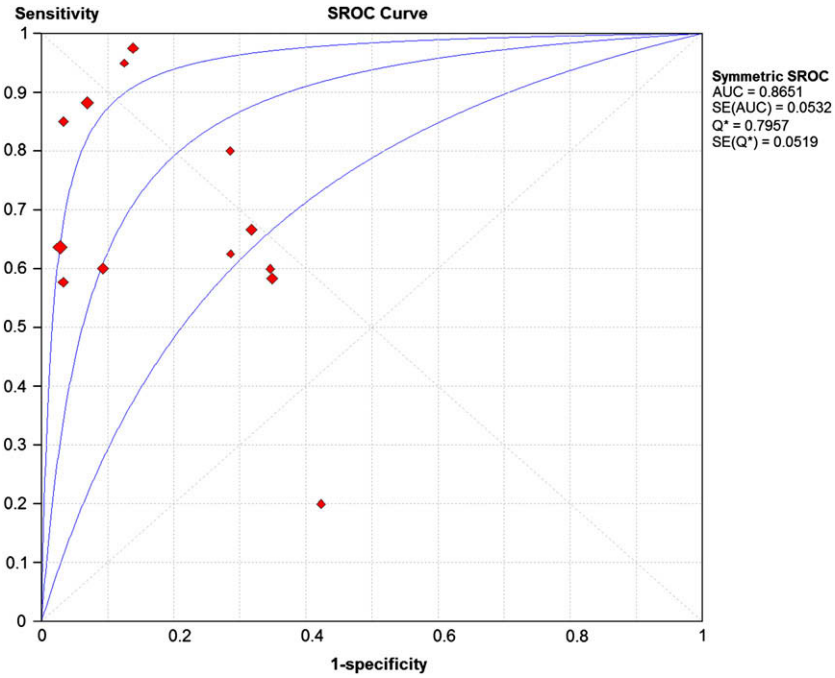

Fig 3. Summary receiver operator characteristic curve of PCT as a predictor of development of SAP.

among the studies, notably with regard to the timing and method of PCT measurement as well as the cutoff values used to define SAP in the literature. In addition, the fact that 3 different methods were used to measure PCT (2 different assays and 1 strip test) contributed to this heterogeneity (Table I); however, subgroup analysis revealed that once adjusted for quality of studies and cutoff values of PCT used, the degree of heterogeneity among studies was no longer statistically significant.

As for any other biologic marker of severity, the accuracy of PCT seems to be dependent on cutoff values and timing of assays as well as the size and quality of studies (Table I). Although no consensus exists regarding the most appropriate cutoff value for identification of SAP, a sensitivity analysis suggests that a value greater than 0.5 ng/mL seems to be an accurate predictor of severity without significant heterogeneity among the studies that used this cutoff value (Table III). Almost all the studies included in this meta-analysis measured PCT on admission and for several days afterward, with some of these studies performing daily PCT levels for up to 14 days. PCT assays measured within 24 h of admission were used for the prediction of severity of acute pancreatitis, whereas studies evaluating the value of PCT as a predictor of infected pancreatic necrosis involved daily repeated PCT measurements using the greatest PCT value among repeated measurements to identify patients likely to develop infected pancreatic necrosis (Table I). Therefore, it is possible to tailor the timing and number of PCT levels performed in each patient to the clinical need.

Several authors performed serial daily serum PCT measurements and reported that patients who subsequently developed infected pancreatic necrosis had a sustained increase in serum PCT levels[13,14,20,33,34]; the degree of PCT increase reflected the severity of systemic inflammatory response and multiorgan dysfunction. In addition, serum PCT levels seem to fall with clinical improvement. Rau et al[13] reported that nonsurvivors exhibited a similar sustained increase in serum PCT levels, which remained increased until the patients demise.

PCT was found to be an accurate predictor of development of infected pancreatic necrosis (Figs 4–6); in contrast to the heterogeneity that was observed among the studies that evaluated the value of PCT as a predictor of development of SAP, no significant heterogeneity was observed in the studies that evaluated PCT in prediction of the development of infected pancreatic necrosis. This prediction is clinically important because patients with sterile pancreatic necrosis are treated conservatively, whereas infected pancreatic necrosis generally requires surgical or radiologic intervention.[45] Infected pancreatic necrosis is often diagnosed by microbial culture of material obtained using image-guided FNA of pancreatic tissue.[46,47]

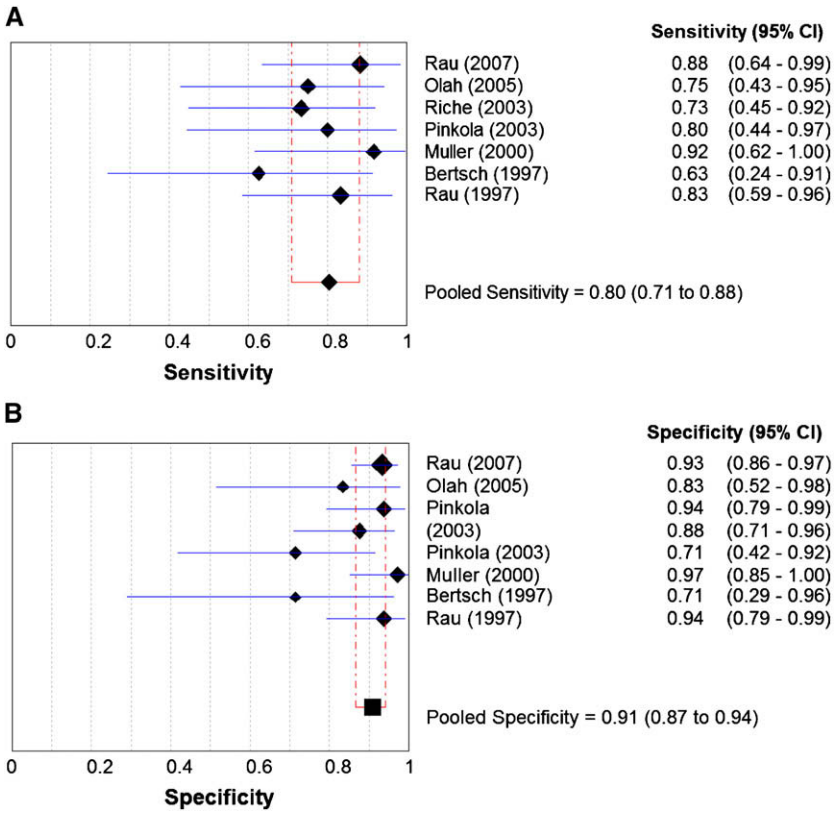

Fig 4. Pooled sensitivity (*A*) and specificity (*B*) of PCT as a predictor of development of infected pancreatic necrosis.

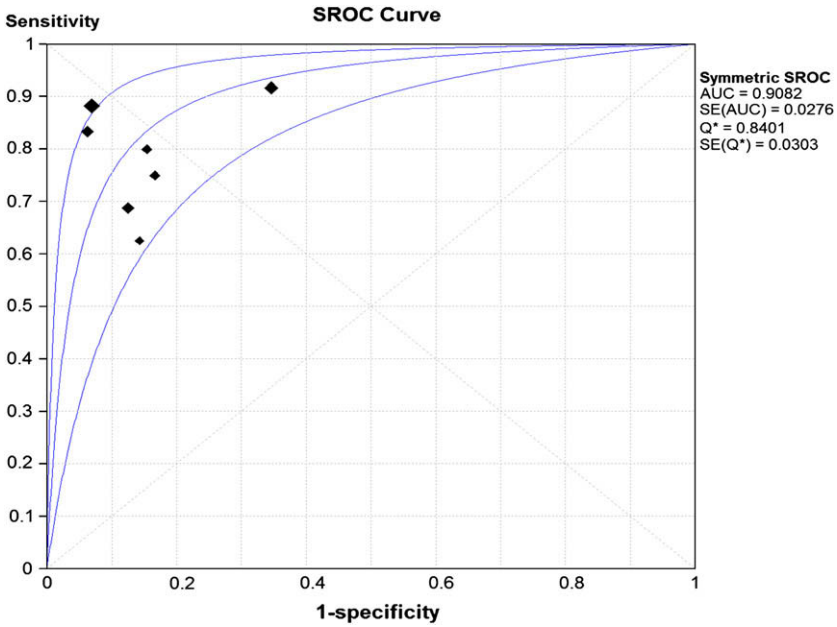

Fig 5. SROC curve of PCT as a predictor of development of infected pancreatic necrosis.

Unlike FNA, the measurement of serum PCT level is noninvasive and is not associated with the potential of sampling error. Furthermore, bacterial and fungal cultures require 48 h of incubation and can be affected by concurrent use of broad spectrum antibiotic or antifungal therapy, whereas serum PCT remains increased in patients with infected pancreatic necrosis.[13,20]

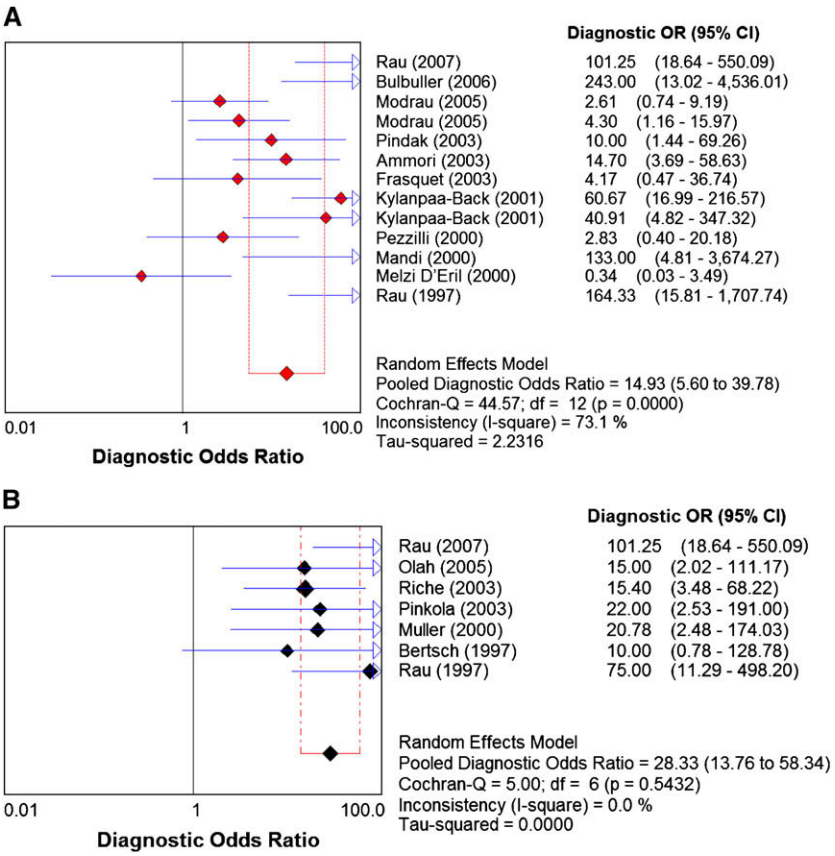

Fig 6. Diagnostic odds ratio of procalcitonin as a predictor of SAP (*A*) and infected pancreatic necrosis (*B*).

Table III. Sensitivity analysis for studies assessing the accuracy of PCT as a predictor of severity of acute pancreatitis

Study subgroups	*Number of studies*	*Number of patients*	*DOR (95% CI)*	*AUC*	*Q*	P *value*
Outcome of interest: development of SAP	2	826	14.9 (5.6–39.8)	0.87	28.6	<.01
Study size >50 patients	0	734	27.0 (10.4–70.1)	0.90	26.9	.008
Year of publication ≥2001	1	781	17.1 (6.2–47.0)	0.86	26.5	.0009
STARD quality score >16		700	32.8 (10.1–106.6)	0.91	3.85	.26
PCT sampled within 1st 24 h		832	15.2 (4.0–27.1)	0.87	33.4	<.001
Cutoff PCT level >0.5 ng/mL	3	897	30.7 (10.7–87.8)	0.88	7.83	.08
Outcome of interest: infected pancreatic necrosis		329	28.33 (13.8–58.3)	0.91	5.00	.54
Outcome of interest: mortality		288	26.1 (10.1–48.2)	0.89	3.21	.61

It is, however, important to remember that PCT is a nonspecific marker of infective complications in critically ill patients[13]; therefore, increased serum PCT levels will not provide any information about the underlying source of infection, and other infective foci such as the respiratory tract, urinary tract, or catheter-related infections need to be excluded carefully when interpreting PCT measurements.[13] Interestingly, Rau et al[13,20] observed that the most marked increase in PCT occurs as a result of abdominal infections, and other sources of sepsis, such as chest and urinary tract infections had a less dramatic effect on serum PCT levels.

The use of antibiotic prophylaxis in patients with necrotizing pancreatitis remains a controversial issue. It has been subject to scrutiny by many meta-analyses[48-50] and randomized controlled

trials[51-56] with the evidence suggesting that antibiotic prophylaxis may be associated with a decrease in the incidence of septic complications and mortality.[48,49] Procalcitonin as an early predictor of development of infected pancreatic necrosis can identify those patients who are at greatest risk and would potentially benefit from prophylactic antibiotic therapy.

In conclusion, serum procalcitonin measurements may be valuable in predicting the severity of acute pancreatitis and the risk of developing infected pancreatic necrosis. Although the exact place of PCT in the management of patients with acute pancreatitis remains to be defined, serum PCT as an early marker of development of infected pancreatic necrosis can be a useful adjunct to conventional severity stratification and be a guide to the progress of the disease.

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