Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis

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Objective: **To quantify the accuracy of serum procalcitonin as a diagnostic test for sepsis, severe sepsis, or septic shock in adults in intensive care units or after surgery or trauma, alone and compared with C-reactive protein. To draw and compare the summary receiver operating characteristics curves for procalcitonin and C-reactive protein from the literature.**

Data Source: **MEDLINE (keywords: procalcitonin, intensive care, sepsis, postoperative sepsis, trauma); screening of the literature.**

Study Selection: **Meta-analysis of all 49 published studies in medical, surgical, or polyvalent intensive care units or postoperative wards. Children, medical patients, and immunocompromised patients were excluded.**

Data Extraction: **Thirty-three studies fulfilled inclusion criteria (3,943 patients, 1,828 males, 922 females; mean age: 56.1 yrs; 1,825 patients with sepsis, severe sepsis, or septic shock; 1,545 with only systemic inflammatory response syndrome); eight studies could not be analyzed statistically. Global mortality rate was 29.3%.**

Data Synthesis: **Global odds ratios for diagnosis of infection complicated by systemic inflammation were 15.7 for the 25 studies (2,966 patients) using procalcitonin (95% confidence interval, 9.1–27.1) and 5.4 for the 15 studies (1,322 patients) using C-reactive protein (95% confidence interval, 3.2–9.2). The summary receiver operating characteristics curve for procalcitonin was better than for C-reactive protein. In the 15 studies using both markers, the Q* value (intersection of summary receiver operating characteristics curve with the diagonal line where sensitivity equals specificity) was significantly higher for procalcitonin than for C-reactive protein (0.78 vs. 0.71, $p = .02$), the former test showing better accuracy.**

Conclusions: **Procalcitonin represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock, difficult diagnoses in critically ill patients. Procalcitonin is superior to C-reactive protein. Procalcitonin should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units. (Crit Care Med 2006; 34:1996–2003)**

KEY WORDS: procalcitonin; biological marker; sepsis; septic shock; intensive care unit; postoperative complications; trauma; diagnostic test; meta-analysis

Infections are a major cause of death among critically ill patients. Early diagnosis and assessment of the systemic inflammatory response to infection, crucial to management and outcome of these patients, are difficult with usual markers (fever, leukocytosis, C-reactive protein [CRP]). Although bacterial culture is the best method for diagnosis of infection, it does not indicate the host response well or differentiate between bacterial colonization and systemic complications like a systemic inflammatory response to infection or invasive bacterial infections. Markers like procalcitonin (PCT) or CRP respond both to infection and inflammation and hence reflect both microbiological findings and the host response, which have significant influence on prognosis and outcome. However, since they are "indirect" markers of infection, their sensitivity and specificity for diagnosis of infection are not 100% and vary in different patient groups and indications. PCT was first found elevated in sepsis in 1993 (1). PCT is synthesized physiologically by thyroid C cells but in sepsis has an extrathyroidal origin. After intravenous injection of endotoxin from *Escherichia coli* to healthy volunteers, serum PCT becomes detectable at 4 hrs, maintaining a plateau through 8 and 24 hrs, following an increase of proinflammatory cytokines (tumor necrosis factor-α, then interleukin-6) (2). PCT normalizes more rapidly than CRP. Whether PCT is more specific for infection than cytokines is still debatable. Presently, a number of studies point out that PCT is a superior marker than CRP for diagnosis of sepsis and/or infection, but some authors disagree (3). An updated meta-analysis of studies is therefore needed.

PCT may be elevated in nonseptic systemic inflammatory response syndrome (SIRS) (4–6) and immediately after surgery (5) or trauma (7), without obvious infection. Its best established indications are bacterial meningitis in children (8) and sepsis in critically ill patients. PCT is ubiquitously expressed in sepsis (9). Our meta-analysis aimed to determine whether PCT is a useful diagnostic marker of sepsis, severe sepsis, or septic shock in adult intensive care units (ICUs) or after surgery or multiple trauma, compared with nonseptic SIRS. We also wished to compare the diagnostic performance of PCT and CRP.

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Recently, a first meta-analysis was published comparing the accuracy of PCT and CRP used simultaneously for diagnosis of bacterial infection (10). It included a limited number of pediatric and adult studies, not always in critically ill patients, with one study in immunosuppressed patients. It only included studies published before June 2002; since then, many more studies have been reported (11–22). Among all studies published (11–59), the performance of PCT diagnostic tests varies considerably. We therefore continued our work, focusing on a more homogeneous recruitment of septic patients in ICUs.

MATERIALS AND METHODS

Publication Selection. Our study protocol was written in November 2003. To be eligible, studies had to have explicitly used PCT as a diagnostic test in ICUs or after surgery or trauma. We only included articles written in English or French. Studies were identified by an electronic search of MEDLINE online via PubMed, with each of the following sequences of key words: "procalcitonin, intensive care, sepsis"; "procalcitonin, postoperative sepsis"; and "procalcitonin, trauma." The last query was updated in October 2004. We also screened references from the relevant literature including all identified studies. We avoided duplication of data, examining for each publication authors and medical centers. We asked Brahms Diagnostica GmbH (Berlin, Germany), the only provider of commercial kits for PCT assay, whether they had unpublished data (they had not). When needed, corresponding authors were requested by e-mail or letter to provide us with additional data.

Methodological Assessment. Information was carefully extracted from articles by two readers (BU and RC) using a standardized data collection form with the following items: complete reference, prospective or retrospective design, inclusion of consecutive patients, blinded caregivers (ignoring results of PCT assays), receiver operating characteristics (ROC) curve (best way to choose the optimal cutoff value of PCT) (60, 61), sensitivity and specificity for PCT (and, whenever available, CRP) as diagnostic tests for systemic infection, type of ICU (medical, surgical, or polyvalent), time when PCT was sampled (on admission, during stay in ICU), number of patients, gender, mean age, median duration of stay in ICU, rate of positive blood cultures among infected patients, and mortality rate.

We did not set a minimal number of patients to include a study or a minimal duration of follow-up. We did not weigh each study by a quality score, since no score received general agreement for meta-analyses of observational studies. Studies were not blinded to readers; rejection was always decided by consensus.

In most studies, "sepsis" comprised sepsis, severe sepsis, and septic shock. We thus used the term *sepsis* in a broader sense than in ACCP/SCCM criteria (62). We defined nonseptic SIRS as a systemic inflammatory response syndrome where no source of infection was found and noninfectious conditions (burns, pancreatitis) caused SIRS.

Statistical Methods. We used a three-step approach based on summary ROC (SROC) curves with an unweighted model (63, 64), using linear regression to combine data from independent studies. First, for each study, sensitivity (Se) and specificity (Sp) were calculated from the 2 × 2 table of contingency, adding when needed 0.5 to all counts in the table as a conventional correction for zero count. Se and Sp being interdependent, a combined indicator was built, diagnostic accuracy (DA), representing the odds of positivity in target infected patients relative to the odds of positivity in nontarget patients. The higher the global odds ratio (OR), the closer the SROC curve to upper left corner of the ROC space. Equations were

$$\text{Se or TPR (true positive rate)} = TP/(TP + FN) \quad [1]$$

where TP and FN were true positive and false negative counts, respectively,

$$\text{Sp or TNR (true negative rate)} = TN/(TN + FP) \quad [2]$$

where TN and FP were true negative and false positive counts, respectively.

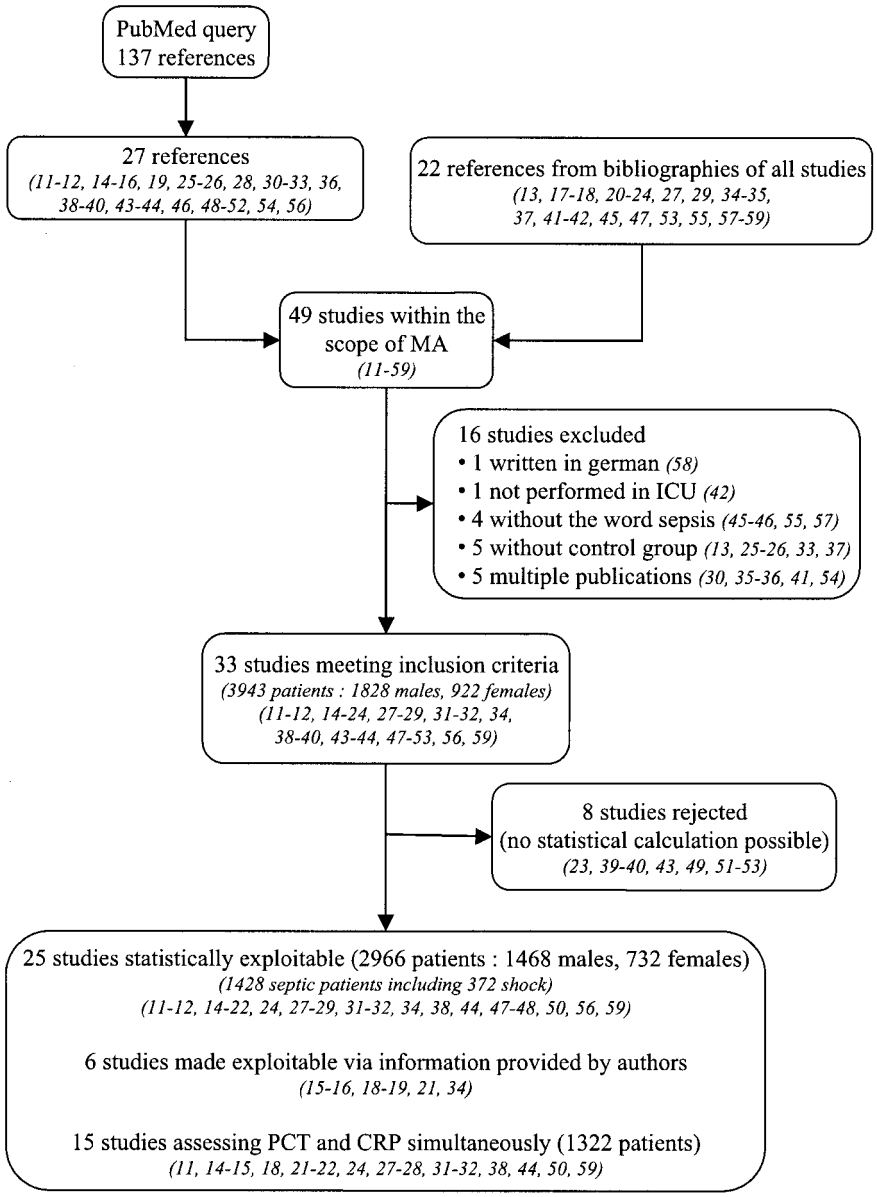

Figure 1. Flow chart of the meta-analytic process. *MA*, meta-analysis; *ICU*, intensive care unit; *PCT*, procalcitonin; *CRP*, C-reactive protein. (References of studies are in parentheses.)

Table 1. Main characteristics of the studies eligible and assessed for meta-analysis

First Author Year of Issue (Reference No.)	Type of Patient	C	Blinded Study	Eligible/Assessed	N
Castelli 2004 (11)	SIRS vs. sepsis Polyvalent ICU	C	Yes	Assessed	150
Clec'h 2004 (12)	Septic shock vs. nonseptic shock Polyvalent ICU	C	?	Assessed	75
Balci 2003 (16)	SIRS vs. sepsis Polyvalent ICU	C	Yes	Assessed (authors)	33
De Talance 2003 (17)	SIRS vs. sepsis Medical ICU	?	Yes	Assessed	108
Du 2003 (14)	SIRS vs. sepsis Polyvalent ICU	C	Yes	Assessed	51
Geppert 2003 (18)	Septic shock vs. cardiogenic shock Cardiac ICU	?	?	Assessed (authors)	55
Luzzani 2003 (15)	Polyvalent ICU	C	?	Assessed (authors)	70
Giamarellos-Bourboulis 2002 (20)	SIRS vs. sepsis Polyvalent ICU	?	?	Assessed	119
Ruokonen 2002 (21)	SIRS vs. sepsis Polyvalent ICU	C	?	Assessed (authors)	208
Tugrul 2002 (22)	SIRS vs. sepsis Polyvalent ICU	?	Yes	Assessed	85
Harbarth 2001 (24)	SIRS vs. sepsis Polyvalent ICU	C	Yes	Assessed	78
Yukioka 2001 (23)	SIRS vs. sepsis Medical ICU	C	Yes	Eligible	35
Brunkhorst 2000 (29)	Medical ICU	C	Yes	Assessed	185
Cheval 2000 (27)	Septic shock vs. nonseptic shock Polyvalent ICU	C	Yes	Assessed	60
Müller 2000 (32)	Medical ICU	C	Yes	Assessed	101
Oberhoffer 2000 (34)	SIRS vs. sepsis Surgical ICU	C	?	Assessed (authors)	242
Selberg 2000 (31)	SIRS vs. sepsis Medical ICU	?	?	Assessed	33
Suprin 2000 (28)	SIRS vs. sepsis Medical ICU	C	Yes	Assessed	101
Ugarte 1999 (38)	SIRS vs. sepsis Medical ICU	C	?	Assessed	205
Whang 1998 (39)	Polyvalent ICU	C	?	Eligible	29
De Werra 1997 (40)	Septic vs. cardiogenic shock Medical ICU	?	?	Eligible	29
Hensler 2003 (19)	SIRS vs. sepsis Trauma/surgical ICU	C	?	Assessed (authors)	137
Wanner 2000 (48)	SIRS vs. sepsis Trauma	C	No	Assessed	405
Benoist 1998 (56)	SIRS vs. sepsis Trauma/surgical ICU	C	?	Assessed	21
Dorge 2003 (44)	Cardiac surgery +CPB/surgical ICU	C	?	Assessed	80
Kabir 2003 (43)	SIRS vs. sepsis Polyvalent ICU	C	?	Eligible	15
Meisner 2002 (47)	SIRS vs. sepsis CABG + prosthesis + CPB/surgical ICU	C	Yes	Assessed	208
Adamik 2000 (49)	Cardiac surgery +CPB/surgical ICU	?	?	Eligible	83
Aouifi 2000 (50)	Surgical ICU	?	Yes	Assessed	97
Baykut 2000 (51)	SIRS vs. sepsis Cardiac surgery +CPB/surgical ICU	C	?	Eligible	400
Boeken 2000 (52)	SIRS vs. sepsis Cardiac surgery +CPB/surgical ICU	No	?	Eligible	74
Reith 2000 (53)	SIRS vs. sepsis Surgical ICU	No	?	Eligible	312
Rothenburger 1999 (59)	Cardiac surgery +CPB/surgical ICU	C	?	Assessed	59

C, the study included consecutive patients; PCT, procalcitonin; CRP, C-reactive protein; M, male; F, female; SIRS, systemic inflammatory response syndrome; ICU, intensive care unit; CPB, cardiopulmonary bypass; CABG, coronary artery bypass graft; assessed study means a study where meta-analytic calculations could be performed for PCT; (authors) means that the study could be assessed thanks to additional data provided by authors.

$$\text{False positive rate (FPR)} = 1 - \text{TNR} \quad [3]$$

$$\text{DA odds ratio (OR)} = [\text{TPR}/(1 - \text{TPR})]/[\text{FPR}/(1 - \text{FPR})] \quad [4]$$

In addition, standard calculations to obtain 95% confidence intervals (CIs) for range estimates were applied to the DA OR. This approach allowed us to use a random effect model (Der Simonian and Laird), more conservative than the Mantel Haenszel procedure and more suited to heterogeneous data.

In the second step, we calculated D (difference) and S (sum) for each study. D measured the discriminating power between patients with and without infection, S the positivity threshold:

$$D = \log[\text{TPR}/(1 - \text{TPR})] - \log[\text{FPR}/(1 - \text{FPR})] \quad [5]$$

$$S = \log[\text{TPR}/(1 - \text{TPR})] + \log[\text{FPR}/(1 - \text{FPR})] \quad [6]$$

The third step was the construction of the summary ROC curve using a simple linear regression model between individual Di (dependent variable) and Si (predictor variable), as:

$$D = a + b * S \quad [7]$$

Then, the fitted regression line was back-transformed into the conventional axes (TPR vs. FPR) to describe the summary ROC curve across the combined studies. The intercept (a) was the estimated logarithm of the global DA OR assuming a constant accuracy of the test between studies. The slope (b) provided an estimate of the extent to which logOR depended on the study (65).

To compare the performances of PCT and CRP, we used Q* values from the SROC curves (64), corresponding to their intersection with the diagonal line where sensitivity equals specificity (66).

All statistical calculations were performed using the R and S environments for statistical computing and graphics (www.r-project.org). By convention, $p < .05$ was considered statistically significant.

RESULTS

Study Selection and Characteristics. The flow chart of our meta-analysis is shown in Figure 1. Our global literature search collected 49 studies (11–59). One study included was a short report written in French (17). One publication, written in German with an English abstract mentioning SIRS and sepsis, did not contain the data needed for inclusion (58). All other articles were written in English. Our last reference (59) was found in the previous meta-analysis (10), which included only six of our 15 articles studying PCT and CRP (28, 31, 32, 38, 50, 59).

Cutoff		Sensitivity, %		Specificity, %						
PCT, ng/mL	CRP, mg/L	PCT	CRP	PCT	CRP	Nonseptic SIRS, No.	Septic Shock, No.	Total Sepsis, No.	Gender, M/F	Death, No. (%)
1.11	128	79	67	85	82	15	15	71	96/54	29/150 (19)
1		95		54		13	62	62	51/24	50/75 (67)
2.97	145	82	58	100	58	12	6	21	17/16	10/33 (30)
2		91		89			27	90	76/32	31/108 (28.7)
1.6	75	80	80	74	29	31	10	20	31/20	13/51 (25)
2	91.5	87	100	75	65	40	15	15	41/14	36/55 (65.5)
2	50	76	89.5	84	75			38	?	14/70 (20)
1		94.5		64.5		29	10	38	84/35	43/119 (36)
0.8	154	68	50	48	74	46	25	162	?	66/208 (31.4)
1.3	39	73	35	83	42	10	41	75	39/46	40/85 (47)
1.1	150	97	68	78	73	18	25	60	57/21	27/78 (34.6)
						16	12	19	22/13	11/35 (31.4)
2		96		86		17	39	168	?	52/185 (28)
5	100	88	93	67	40	28	16	32	34/26	21/60 (35)
1	100	89	71	94	78			58	55/46	23/101 (23)
1.35		84		83		117	45	70	152/90	
3.3	60	86	86	54	18	11		22	20/13	16/33 (59)
2	100	65	74	70	74	20	24	75	63/32	30/95 (31.6)
0.6	79	68	72	61	67	79		111	124/66	53/190 (27.9)
1.08		67		80						14/29 (50)
							15	22	18/11	
1.5		42		73		45		88	102/35	15/137 (11)
1.5		75.5		77		161		45	301/104	93/405 (23)
5	150	100	69	100	31	12		4	?	1/21 (5)
5		63		62		53		27	55/25	17/80 (21.3)
						5		10	12/3	
2		87		78		193		15	?	
						42	20	41	24/17	25/41 (61)
1	150	85	64	95	84	43	12	54	70/33	
						364		27	269/131	
						15		15	15/15	
0.8						66		246	?	59/246 (24)
4	180	86	100	98	75	44		7	?	

Main characteristics of studies are presented in Table 1. Global mean age was 56 yrs, ranging from 29 in a trauma study (56) to 66.5 in a polyvalent ICU (15). The 33 independent studies meeting inclusion criteria included 1,825 infected patients and 1,545 nonseptic SIRS patients, the rest being nonseptic non-SIRS controls. Global mortality rate was 29.3%. Pooled percentage of patients with positive blood cultures was 24.9%. All studies but one (18) had a prospective design, and in only 12 studies, observers were blinded to the results of PCT (11, 14, 16, 22–24, 27, 28, 32, 38, 47, 50). In 23 studies, the authors explicitly recruited a consecutive series of patients (11, 12, 14–16, 19, 21, 23, 24, 27–29, 32, 34, 38, 39, 43, 44, 47, 48, 51, 56, 59). Studies lasted from 3 (15) to 60 months (19). In four studies, we could only include septic shock compared with shock from another cause (12, 18, 27, 40). PCT was always obtained on admission or early in the course of sepsis but usually also during the first week after admission, sepsis, or surgery. Calculations were impossible (2 × 2 table of contingency not available) in eight studies (23, 39, 40, 43, 49, 51–53). We asked for additional data from 18 studies and received information allowing meta-analysis for six studies (15, 16, 18, 19, 21, 34) and exclusion for one (25).

In all studies in the meta-analysis, PCT was measured with the same immunoluminometric assay (LUMItest PCT; Brahms Diagnostica GmbH, Berlin, Germany). With this method, the functional detection limit was 0.3 ng/mL with a 20% interassay coefficient of variation. No study used the more recent method for Kryptor (automated immunofluorescent assay with TRACE, Time Resolved Amplified Cryptate Emission technology). Methods to determine CRP differed between studies.

Meta-Analysis. From the 25 studies using PCT (2,966 patients), sensitivities ranged from 42% (19) to 97% (24) or even 100% (56) and specificities ranged from 48% (21) to 100% (16, 56). The optimal cutoff values for PCT, determined from the ROC curves, ranged from 0.6 (38) to 5 ng/mL (27, 44, 56) (Table 1).

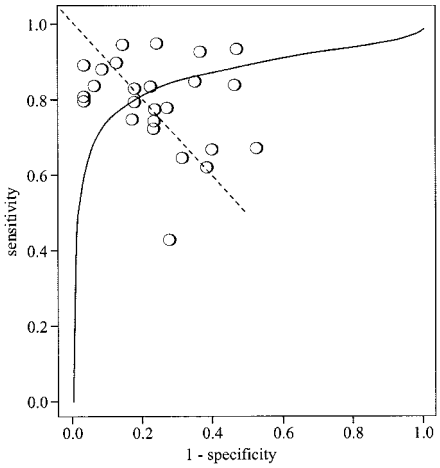

Figure 2. Summary receiver operating characteristics curve for procalcitonin, according to Moses and Littenberg model; n = 25 studies.

The global summary ROC curve for all 25 studies which used PCT is shown in Figure 2. When infection was compared with nonseptic SIRS, PCT had a global DA OR of 15.7 (95% CI, 9.1–27.1, $p < .0001$). This means that the risk for a

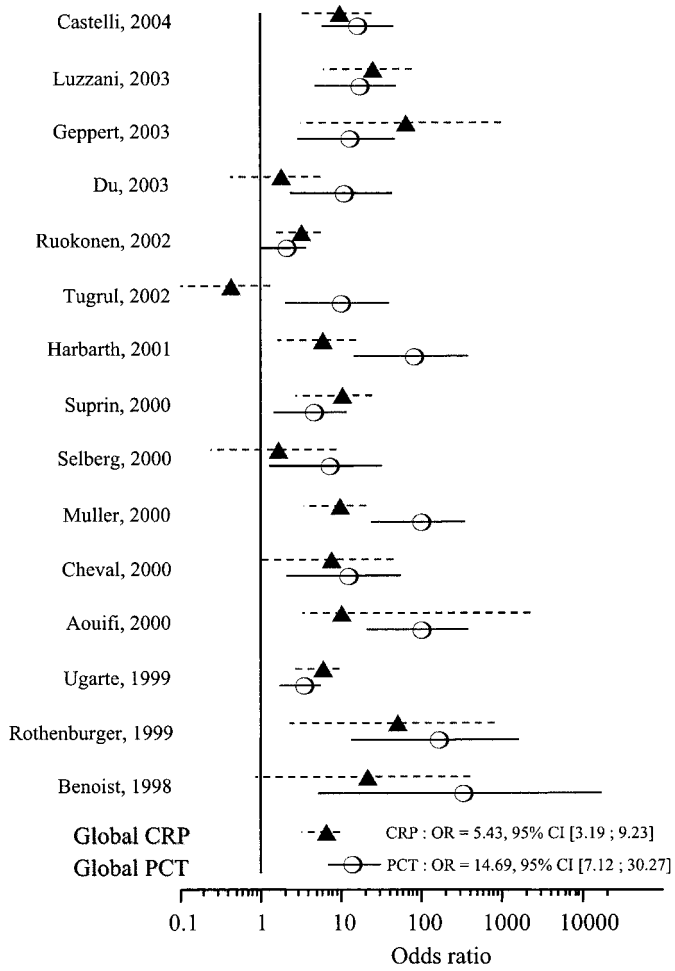

Figure 3. Global diagnostic accuracy odds ratios for procalcitonin (*PCT, circle, solid line*) and C-reactive protein (*CRP, triangle, dashed line*); n = 15 studies. *OR*, odds ratio; *CI*, confidence interval.

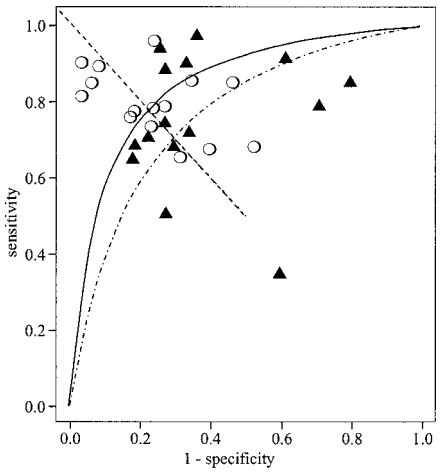

Figure 4. Summary receiver operating characteristics curves for procalcitonin (*circle, solid line*) and C-reactive protein (*triangle, dashed line*), according to Moses and Littenberg model; n = 15 studies.

positive PCT test in infected patients was about 16-fold higher than in noninfected patients. In the separate analysis of the 15 studies (1,374 patients) assessing CRP, sensitivities ranged from 35% (22) to 100% (18, 59), and specificities ranged from 18% (31) to 85% (11). Cutoff values for CRP ranged from 39 mg/L (22) to 180 mg/L (59).

Global DA ORs for the 15 studies assessing both PCT and CRP are presented in Figure 3 and corresponding SROC curves in Figure 4. PCT had a global DA OR of 14.7 (95% CI, 7.1–30.3, $p < .0001$). CRP had a global DA OR of 5.4 (95% CI, 3.2–9.2, $p < .0001$). Thus, both tests diagnosed infection efficiently. Statistical comparison of the two ORs for PCT and CRP showed that PCT had a greater accuracy than CRP (ratio of the global ORs = 2.7; $p = .01$). This is confirmed graphically in Figure 4, since the PCT SROC curve is always above the corresponding curve for CRP. These results were qualitatively improved when the analysis was restricted to the blinded studies: global DA OR PCT = 28.6 (n = 12), global OR CRP = 4.5 (n = 8); ratio of ORs for the eight common studies = 4.6 ($p = .01$).

The Q* values offered another way to compare PCT and CRP accuracies. Again, PCT performed significantly better than CRP (Q* value for PCT = 0.78; 95% CI, 0.71–0.84 vs. Q* value for CRP = 0.71; 95% CI, 0.64–0.76; corrected $p = .02$, computed under the conservative hypothesis of a .5 correlation coefficient between PCT and CRP values). Q* value equals 1 for fully discriminating tests and 0.5 for nondiscriminating tests. For the subgroup of blinded studies, Q* for PCT and CRP was 0.8 and 0.69, respectively ($p = .02$).

DISCUSSION

Our article complies with the recommendations for reporting meta-analyses of diagnostic tests (67, 68). Diagnosis of sepsis has no "gold standard" in critically ill patients. Microbiological culture lacks sensitivity and specificity (colonization) and takes ≥24 hrs. Although international definitions of sepsis, severe sepsis, and septic shock exist (62), these diagnoses may vary according to individual clinical experience. Consequently, a specific biological marker would be very useful, especially if, like PCT, it was stable in blood samples, was easy to perform, was not too expensive, and provided a quick answer (30 mins for automated PCT assay on Kryptor using TRACE technology, more sensitive than the luminometric assay used in all studies in the meta-analysis). However, in critically ill patients, the global performance of PCT is far from ideal, as shown by its SROC curve (Fig. 2) but better than CRP (Fig. 4), which reflects mainly inflammation. However, CRP is prescribed systematically in ICUs, whereas PCT is not universally used.

Meta-analyses of diagnostic tests do not have the same strength as those of randomized controlled trials, because studies have usually a poorer methodology (66). They offer statistical challenges, due to the bivariate nature of the expression of test performance. Simple pooling of individual sensitivities and specificities, ignoring threshold differences, is inappropriate. The authors of the formerly published meta-analysis did not specify how they obtained their global sensitivities and specificities (10). We used a random effect model, assuming that diagnostic accuracy of the test varied between studies and the various degrees of accuracy were randomly distributed among a central value represented by the SROC curve.

Like meta-analyses of diagnostic tests, our work has limitations (69, 70). Publi-

cation bias (lower probability of publication of negative results) seems harder to avoid than in meta-analyses of randomized controlled trials. The quality of studies included in our meta-analysis appeared rather good, probably because they were recent. However, in each study, the characteristics of the study population and the "blindness" of design (12 studies) were often not fully reported, the expertise of the reader of the test was never reported, and the details of the analytical validation of the test were not reported. Several studies did not explicitly include consecutive series of patients, potentially creating a distorted selection of participants. By pooling studies dealing with various samples, clinical settings, and prognoses, we might have introduced excessive heterogeneity, since diagnostic tests may have different accuracies at various phases of a disease. Therefore, we chose to limit our spectrum of infected patients to critically ill nonimmunocompromised adults. Most included studies used the term *sepsis* as a mixture of sepsis, severe sepsis, and septic shock, compared with nonseptic SIRS, with possible misclassification between both diagnoses (inappropriate reference standard bias). Moreover, should localized infections be considered as cases or controls, knowing that PCT is usually almost normal? Although PCT determination always occurred on admission or during the first day after infection, only nine studies (14, 16, 18, 27, 29, 31, 40, 44, 47) analyzed exclusively these early data. Other studies seemed to pool results of various time samples. Thus, our meta-analysis cannot strictly conclude that early PCT determination is more useful for prediction of sepsis, although there are biological grounds favoring this assertion (2). Context bias, the tendency of interpreters to consider test results as positive more often when disease prevalence is high, might also affect estimates of test performance. Verification bias was controlled for: In all studies, PCT and other tests were performed simultaneously.

PCT can now be used as a quick and early diagnostic test of sepsis in critically ill nonimmunocompromised adults. A quick assay is more suitable for emergency decision making. Considering all exploitable studies, we showed that PCT has a greater accuracy than CRP in this context. As a screening test, PCT could help decide which patients are likely infected and thus should be offered multiple cultures and empirical antibiotic therapy. Increased PCT also indicates a systemic inflammatory host response to infection, probably endangering the patient by an increased risk of organ dysfunction. Future studies should follow the recent recommendations of STARD (STAndards for Reporting of Diagnostic accuracy) initiative (71): include enough patients and better describe study population. PCT is not a gold standard for infection but may make this diagnosis easier, especially in the emergency context of systemic inflammation or shock. PCT should find its place in the guidelines for evaluation of diagnosis and prognosis of sepsis in critically ill patients. The PIRO concept (Predisposing conditions, Infection, host Response, concomitant Organ dysfunction) already suggests PCT for diagnosis of sepsis (68). In this population, would the diagnostic accuracy of PCT be sufficient to help decide which patients should be treated with antibiotics, as already shown in patients with lower respiratory tract infections (72)? Considering the current overuse of antimicrobial agents, this attitude would result in a decrease in their side effects, lower costs, and reduced emergence of drug resistance.

Addendum. Our last update of online PubMed retrieved a reference we could not include (73). During the first days of their stay in an adult ICU, 123 consecutive patients with SIRS (median age 61 yrs; 31% died in hospital) had PCT and CRP assays. For the diagnosis of sepsis based on bacteremia (90 missing data!), cutoff values of 3 ng/mL for PCT and 185 mg/L for CRP gave sensitivities of 83% and 83% and specificities of 48% and 76%, respectively. We then did an EMBASE query, which retrieved only one additional reference including 11 patients with postoperative sepsis (74). Even later, we were informed about one additional reference including 16 patients with severe trauma (75). We did not add these two references to our meta-analysis since it would not have modified our results (small numbers of patients) but implied time-consuming calculations.

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